SURGERY
Gynecology & Obstetrics
MARCH 1960
VOLUME 110
NUMBER 3

EXPERIMENTAL PRODUCTION OF PHLEBOTHROMBOSIS

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INJURY to the intima of the vascular wall, stasis or turbulence of the blood flow, hypercoagulability of the blood in the general circulation or in one of its districts are known, among other factors, to precipitate venous thrombosis in man (Fig. 1). These factors combine variously to produce the clinical syndrome of thrombophlebitis and phlebothrombosis but their respective role is not fully understood. The importance of intimal injury with or without stasis has been well documented by Zahn (9, 10), Eberth and Schimmelbusch, and Welch by means of careful animal experiments, which find their clinical counterpart in the thrombophlebitis which follows injury or infection of the vascular wall in man. There are, nevertheless, instances of thrombus formation in man (phlebothrombosis) in which no evidence of preceding injury to the intima may be found, although this may eventually develop because of the phlebitic reaction which accompanies intravascular clotting. It is postulated that this type of sudden coagulation of the blood within an apparently intact vascular channel may result from the combined effect of stasis due to outside pressure or to slowing of the blood flow because of circulatory failure—and of a poorly defined, transient "hypercoagulable state." As indicated by Wessler and his associates, a state of transient hypercoagulability may be induced in dogs and other animals by the systemic infusion of thromboplastin, of thrombin, or of homologous serum. If a venous segment is isolated shortly afterward, a clot forms within the isolated segment; also, a clot forms at the site of either a complete or a partial ligature.

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Supported by grant-in-aid from the Massachusetts Heart Association and grant H-2132 (C-2) from the National Institutes of Health.

FIG. 3. Twenty-four hour old specimen: irregular deposition of fibrin enmeshing blood elements. The detachment of the endothelial lining from the vessel wall is artifactitious.

FIG. 5. Seven day old specimen: lines of Zahn. Note also: a, fibroblastic proliferation; and, b, lining of the free margins of the thrombus by endothelium.

FIG. 6. Ten day old specimen: lines of Zahn and partial organization of the thrombus, which is adherent to the vascular wall. Note also: a, thrombus formation within a valve pocket, and, b, a partially organized thrombus in a vessel of the venous wall.

FIG. 9. Six day old specimen: fibrin deposition in the perivascular lymphatics.

FIG. 10. Six day old specimen: perivascular tissue with acute inflammatory reaction and fibroblastic proliferation; endothelium lined channel containing masses of fibrin.

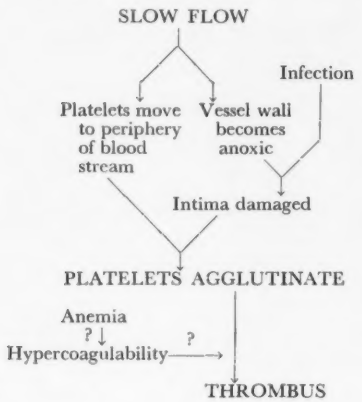

FIG. 1. A hypothesis of the pathogenesis of venous thrombosis.[1]

In the present article is described a modification of the technique introduced by Wessler, which utilizes only partial occlusion of a venous segment and appears to produce phlebothrombosis without obvious injury to the vascular intima. Since the circulation has not been arrested, such technique makes it possible to study the histologic evolution and, more important, to evaluate the clotting changes which accompany the formation and propagation of a venous thrombus. Also our technique and the histologic development of the experimental venous thrombus are described. Subsequent articles will deal with the changes in the blood clotting and in the fibrinolytic system which accompany early formation and the propagation of the clot.

MATERIALS AND METHODS

Thirty dogs were employed in these experiments. Serum was first obtained from blood collected by arterial puncture (femoral) from healthy dogs. It was incubated at 37 degrees C. for 4 hours to allow complete neutralization of thrombin. It was then stored at −20 degrees C. until used. Under aseptic precautions both jugular and femoral veins were exposed in dogs kept under general anesthesia with intravenous pentothal. Segments of both jugular veins and the right femoral vein were isolated. Two partially occluding ligatures were placed around the vessel, over a glass or wooden rod applied alongside, at a distance of approximately 3 centimeters (Fig. 2a). Valves were included between the ligatures when possible. After removal of the rod, the lumen of the vein appeared reduced to approximately one-third of the original (Fig. 2b). A small sac formed within which the circulation of blood continued freely. The left femoral vein was left exposed throughout the procedure but no ties were applied, in order to evaluate the extent of the reaction due solely to the surgical trauma. After all incisions were closed, 15 milliliters per kilogram of weight of homologous canine serum were infused into one of the veins of the foreleg. Another group of 10 dogs received only corresponding volumes of saline solution. Specimens were removed 30 minutes after the injection of serum, then daily for 7 days, on the tenth day, and then weekly for 6 weeks. Thus, 6 specimens were obtained for each time interval. Four additional dogs underwent partial occlusion of both jugular and femoral veins without infusion of serum. Control specimens were removed on the fourth, eighth, and twelfth days.

All specimens were frozen immediately to facilitate cutting in segments and fixed in formol and Zenker's acetic solutions. Multiple serial sections from each specimen were then stained with hematoxylin-eosin, phloxine-methylene blue, and, occasionally, with phosphotungstic acid hematoxylin stains.

RESULTS

Thrombosis (Fig. 2c) developed in 22 of 30 dogs. Macroscopic findings were fairly

[1]This hypothesis does not distinguish between thrombophlebitis and phlebothrombosis. The initial step in thrombosis may be represented by slowing of the blood flow which, in turn, brings platelets from the center to the periphery of the blood stream in contact with the intima. Damage to the intima may be due to infection, to anoxia produced by stasis, or to other mechanisms. Hypercoagulability, as described in this article, is a significant factor in this scheme. Anemia may facilitate hypercoagulability since a small clot at the site of early thrombus formation would be unable to absorb thrombin and thereby prevent furthering of the autocatalytic reaction of blood coagulation. The sequence of events as described here is purely hypothetic; the only purpose of the scheme being the presentation of all significant factors in the pathogenesis of thrombosis.

constant. Thrombi were found in the main lumen of the vessel and more often within the valve pockets at various intervals of time from the infusion of serum. From the fourth day on, the thrombi were clearly adherent to the underlying endothelium. The first totally occluding thrombus was observed on the seventh day. Some of the thrombi had an onion skin appearance because of successive apposition of new layers of fibrin. Increased turgor of the perivascular connective tissue was evident at times between the third and eighth day and had subsided by the end of the second week. Various degrees of thickening of the wall and irregularity of the lumen with narrowing were also present in older specimens. Fresh clots were found at times within the lumen of old recanalized thrombi.

More significant were the histologic findings. No attached thrombus was present during the first 48 hours, as the vein contained only clots of different size and shape, most commonly within the valve pockets. These clots consisted of an irregular reticulum of fibrin with enmeshed formed elements (Fig. 3) and, possibly, clumps of platelets. As early as the third day, lines of Zahn were evident on the side of the clots in contact with the blood stream while they were absent in the clots found within the valvular pockets (Fig. 4). From the fourth day on, the free surfaces oft he thrombus were partially covered with a delicate endothelial lining. Invasion of the clot by fibroblasts began on the fifth day. Fibroblasts grew at first as single cells breaking their way through the fibrin reticulum, later in cords. The largest number of typical thrombi was encountered in 1 to 2 weeks old specimens (Figs. 5 and 6). As a rule, organization and canalization were well advanced by the end of the third week (Fig. 7). Nevertheless, residual changes could still be seen in a few specimens as late as 1 month after the initiation of the process (Fig. 8). Here granulation tissue arose from the intima, or subintimal proliferation of connective tissue was present (phlebosclerosis). In 2 instances, fragments of fresh clot were found within the lumina of the veins involved.

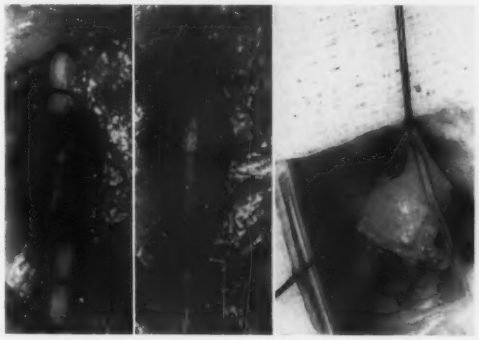

FIG. 2. Procedure for the production of experimental phlebothrombosis in dogs: a, application of partially occluding ligatures; b, partially isolated segment of vein after removal of rods; and, c, open vessel, 3 day old mural thrombus.

Inflammatory reaction of the vascular wall was negligible in most cases. Sparse polymorphonuclear leucocytes appeared occasionally from the third day. By the end of the first week, they were replaced by lymphocytes and plasma cells. At the same time, the presence of large spaces with delicate endothelial lining and packed with abundant fibrin reticulum and, at times, with formed elements of the blood suggested that fibrin thrombi had extended radially into the veins and lymphatics of

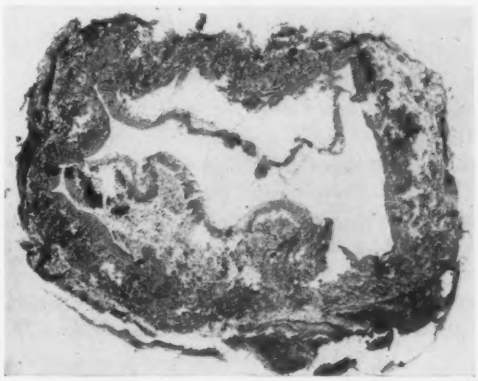

FIG. 4. Five day old specimen: clot with irregular fibrin deposition within a valve pocket of the jugular vein; no lines of Zahn are present.

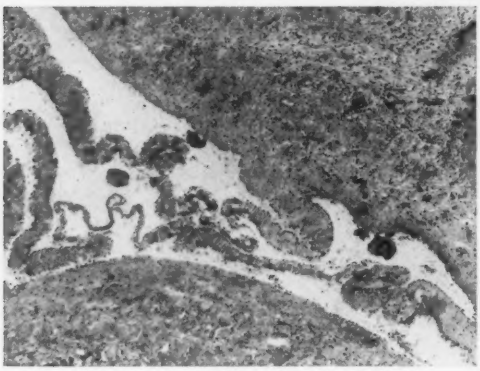

FIG. 7.

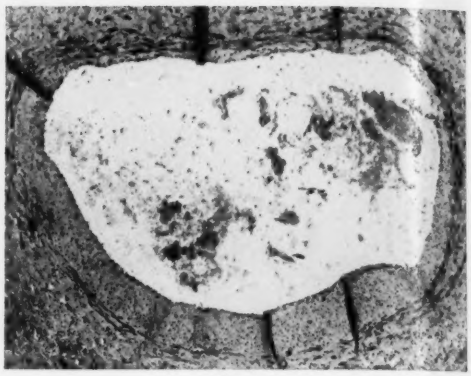

FIG. 8.

FIG. 7. Three week old specimen: extensive fibrosis and recanalization with restitution of the endothelial lining.

FIG. 8. Thirty day old specimen: subintimal proliferation of connective tissue (phlebosclerosis). There are fragments of fresh and organized thrombus in the lumen.

the surrounding tissue (Fig. 9). In less than 1 out of 4 instances, the inflammatory reaction in the vascular wall was somewhat more extensive. Abundant leucocytic infiltration, some edema fluid, and proliferation of fibroblasts were evident. A very striking feature was again the presence of fibrin in many newly formed vascular channels (Fig. 10). Part of the described inflammatory changes might, of course, have been due to the surgical trauma. They were, however, similar to those described by Robertson and associates who injected preformed clots into the portal vein of dogs, an experimental condition excluding to a great extent the possible effect of trauma.

No thrombus developed in any of the dogs in which serum was injected and veins were exposed but not partially ligated. Also, the perivascular reaction was insignificant (Fig. 11). No thrombus developed when partial ligatures were applied but no serum was infused although a corresponding volume of saline solution was administered. Nevertheless, thickening of the vascular wall and various degrees of perivascular fibrosis and scarring were usually noted (Fig. 12).

DISCUSSION

The essential purpose of these investigations is the study of the changes in the blood clotting and fibrinolytic mechanisms which accompany and follow the establishment of phlebothrombosis and the propagation of a venous thrombus. Thus it is essential for the significance of these studies to demonstrate, as done in this article, that phlebothrombosis may be produced by a combination of factors with exclusion of the deliberate primary injury to the vascular intima. Operative procedures such as they are described here may lead to extensive, although not readily demonstrable, alterations of the endothelial lining of the wall of the vessel, as O'Neill has shown, and this, in turn, might favor the formation and propagation of a thrombus. There is no certain experimental way of overcoming this basic difficulty at this time. In our experiments, however, manipulation of a large vein alone without producing stasis and injecting serum was not followed by the formation of a thrombus. On the other hand, the combination of stasis and temporary hypercoagulability sufficed to produce a thrombus which did not develop when the animal was challenged by either factor at exclusion of the other. "Temporary hypercoagulable state" is difficult to define. In our experiments, as will be described in the second article of this series (2), it was produced, as suggested by Wessler and associates, with

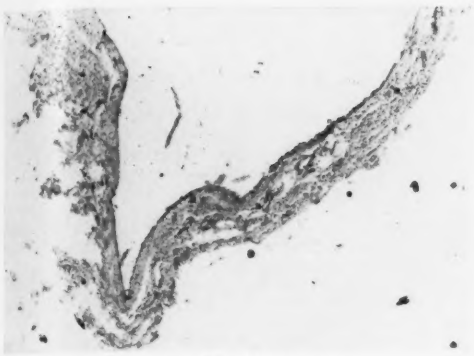

FIG. 11.

FIG. 12.

FIG. 11. Ten day old specimen: note absence of thrombosis and of inflammatory reaction in a vein which had been kept exposed without the application of ties.

FIG. 12. Ten day old specimen: ligatures were applied; saline, not serum was infused. Note thickening and fibrosis of the wall and scanty infiltration of inflammatory cells, without thrombus formation. (Compare with Fig. 10).

the intravenous administration of serum, and it could equally well be produced by the administration of either thromboplastin or thrombin in the proper dose and speed of administration. A more rapid clotting time of recalcified plasma and a faster generation of thromboplastin and thrombin follow the infusion of either reagent, indicating an over-all acceleration of the blood coagulation mechanism. This we consider to represent a hypercoagulability state.

There was considerable similarity between the histologic findings in experimental and human phlebothrombosis. In our animals the thrombus, once formed, continued to develop through stages of organization, recanalization, and fibrosis. The reparative process caused deformity and fibrosis of the vein wall and insufficiency of the valves. New thrombi appeared to form at times in these scarred areas and followed the same evolution. This is essentially the histologic picture of the so-called postphlebitic syndrome in man. In 1 case of 4, phlebitis also developed with a resulting picture simulating that of human thrombophlebitis. These similarities would seem to allow the application of some of the findings obtained here to human pathology, even from a point of view of pathogenetic considerations. In dogs, phlebothrombosis may be produced by stasis but only when a temporary state of hypercoagulability develops. Stasis alone, however, may bring to development a histologic picture of phlebosclerosis but without thrombus formation. In man stasis within the venous system may result from many causes, such as stagnation of blood, as in elderly persons with incompetent venous valves and outside pressure. How temporary hypercoagulability may occur is not entirely clear. Important may be the entrance into the circulation of substances with thromboplastic activity, as it may happen during surgery, after delivery, or when necrotic changes of tissues are present.

It is of interest that phlebitic reaction was found only 3 to 5 days after the initiation of the thrombotic process, and this only in approximately one-fourth of the cases. These results would seem to confirm the clinical impression that phlebothrombosis is detected through objective findings at a fairly late stage of its development (fourth to seventh day) and possibly only when a phlebitic reaction occurs.

SUMMARY

The combination of partial ligature of a large vein and the induction of a state of transitory hypercoagulability of the blood by injection of homologous serum results in

the development of a venous thrombus in dogs. The evolution and propagation of the clot so induced are similar to that observed in human phlebothrombosis and, in some instances, in human thrombophlebitis.

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ACUTE FULMINATING ULCERATIVE COLITIS WITH COLONIC DISTENTION

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THE MAJORITY of patients afflicted with ulcerative colitis present a picture of chronicity from the clinical point of view. The pathologic changes which occur during this period follow a pattern of increasing superficial mucosal ulceration with destruction extending through the muscularis mucosae to the submucosa where replacement fibrosis occurs at a relatively early stage. Even more slowly damage occurs in the main muscle masses of the colon with resultant shortening of the length of the large bowel. The majority of patients with ulcerative colitis are studied and treated by internists and general practitioners along medical lines. A goodly number of these individuals are significantly helped and even cured of their illness without surgical intervention.

This article is presented to draw attention to a small group of cases of ulcerative colitis in which rapid damage takes place, involving all coats of the colon wall. This type of lesion presents itself as an acute fulminating process which may occur at an early stage in the development of the ulcerative colitis or after the process has been present for months or years.

In the course of studying 154 patients with ulcerative colitis admitted to the Hospital of the University of Pennsylvania during a 5 year period from 1953 to 1958, it was noted that the prominent feature of the disease in 9 instances was an acute fulminating course with marked dilatation of the colon mimicking closed loop intestinal obstruction. In view of the paucity of information concerning this type of ulcerative colitis it seemed reasonable to review the cases from our own series as well as those which could be accumulated from the literature so that a clearer understanding of the process as well as its management might be achieved.

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DEFINITION

Acute fulminating ulcerative colitis is a grave form of idiopathic ulcerative colitis. As defined by Bockus, it is employed to describe those cases of acute ulcerative colitis in which "the onset is relatively abrupt and the severity of the attack may reach its peak in 2 to 3 weeks. The attack may continue for weeks or months and terminate fatally, pass into a chronic stage, or into remission." In our series, 6 of the 9 patients suffered an acute attack which terminated in definitive therapy within a period of 1 week or less. The longest interval between the onset of the acute episode and surgical intervention was 3 weeks.

DIAGNOSIS

These patients become acutely ill and exhibit abdominal pain, diarrhea, vomiting, high fever, and prostration with accompanying abdominal distention, tenderness, and diminished or absent peristalic activity. An active ulcerating disease process in the rectum and rectosigmoid areas is almost invariably revealed by proctoscopic examination. The presence of abdominal pain and distention usually prompts an x-ray study which, in addition to providing valuable confirmatory information, may also uncover possible complications of the colonic disease. As McConnell and associates pointed out, because of the severity of the illness and the likelihood of perforation, elaborate

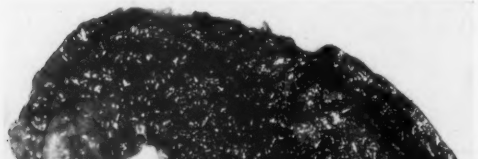

FIG. 1. Colon removed at operation for ulcerative colitis, demonstrating vascular congestion and hemorrhagic mucosa.

roentgenologic procedures are often precluded and one must settle merely for a scout film of the abdomen. The colon is usually seen to contain an excess of gas with the transverse portion showing most marked distention. Thickened, inflamed mucosa may form irregular nodules which protrude into the air filled lumen and cause the outline of the gas shadow to be irregular, nodular, or scalloped. The nodular outline may be seen not only along the margin of the bowel but may be a striking feature in the thickening of the semilunar folds when these have not been effaced by pre-existing chronic colitis. As in chronic colitis, haustral sacculation may be entirely absent even in markedly distended bowels. Considerable distention of the stomach and small bowel may be present, but this is rarely as conspicuous as the accumulation of gas in the colon. In addition, ascites is frequently observed. In McConnell's series 16 of the 26 patients with fulminating colitis exhibited the abnormalities just mentioned. Repeated roentgenograms of the abdomen often bring to light hitherto unseen changes in the wall itself, thus eliminating the necessity for a barium enema. Very rarely does a plain film of the abdomen in the case of fulminating colitis fail to demonstrate some colonic abnormality. The mechanism of the marked colonic distention has been thought to be the combination of a paralytic phenomenon caused by the acute inflammatory reaction in the bowel wall, the putrefaction of colonic contents, and the excessive diffusion of gas through the raw mucosal surface.

PATHOLOGY

The majority of patients afflicted with acute fulminating ulcerative colitis have the disease throughout the colon. The general appearance of the large bowel at operation is that of extensive thinning with markedly dilated areas and vascular congestion producing a weeping, hemorrhagic mucosa. All but 2 of the specimens in our series showed evidence of acute perforation at the time of operation (Fig. 1).

Histologic study of the specimens revealed varying degrees of damage and repair. In all cases, mucosal destruction was extreme with spotty evidence of epithelial regeneration. Capillary dilatation with hemorrhage was noted. Muscle damage varied in degree with primary damage to the outer longitudinal muscle coat (Fig. 2). Warren and Sommers pointed out the intense inflammatory necrosis of the blood vessel walls in their patients with fulminating ulcerative colitis. This resulted in vascular occlusions with infarction of a part or all of the adjacent colon. They stated that the blood vessel lesions closely resembled those in periarteritis nodosa and introduced the term "vasculitis colitis." We have not been impressed with this aspect of the histologic picture. In our series, none of the colon removed for acute fulminating colitis contained any nidus of malignant degeneration, although Ripstein (10) reported that in 2 of his 42 cases carcinoma was a complicating factor of this phase of the disease.

RATIONALE FOR TREATMENT

In the past, only the most conservative methods of treatment were employed for patients with acute fulminating ulcerative colitis. Until recently, medical therapy consisting of rest, blood transfusions, diet, vitamins, antibiotics, steroids, and psychotherapy supplemented by intestinal intuba-

tion has been tried in order to contain this acute process. Ileostomy was employed primarily as a last resort in desperate cases in which it was apparent that medical treatment had nothing further to offer. Since the patients were often moribund, or the colon had perforated before the surgeon was asked to see the patient, it was not surprising that the mortality rate of ileostomy performed for acute fulminating ulcerative colitis was high. Perhaps if ileostomy had been done earlier in such cases, better results would have been obtained, but the fact remains that early operation was not often employed and many patients died of ulcerative colitis either under medical treatment or after an ileostomy performed late in the course of the disease process. Crile and Thomas reviewed the cases of patients with this disease at the Cleveland Clinic between the years 1935 and 1948 and noted that the mortality accompanying medical therapy was 73 per cent, whereas the mortality with ileostomy was 63 per cent when the patients were followed up for reasonably long periods after the onset of the disease. In other reports from the literature as well as from our own experience, the employment of medical therapy or the use of ileostomy alone has represented a poor method of handling this perilous situation (Table II).

It is interesting to note that there is apparently no difference in the mortality of those patients who have acute fulminating colitis of short duration and those who represent an acute exacerbation of chronic disease. In Crile's series there was a 73 per cent mortality for those patients with acute colitis of short duration, whereas there was a 65 per cent mortality for those who experienced an acute exacerbation of a chronic process.

Frequently, the statement has been made that a patient with acute fulminating ulcerative colitis is too sick to withstand a major surgical undertaking. It must be pointed out, however, that if a procedure such as colectomy is accomplished, there results a lessening of the burden of anemia, sepsis, and

FIG. 2. Photomicrograph (×17) of area of colon removed from patient L. K., demonstrating mucosal destruction, capillary dilatation, and marked muscle damage.

metabolic exhaustion due to the removal of the involved area of colon. We agree with Ferguson that the attitude toward these patients should not be that "they are too sick to be operated upon, but rather that they are too sick not to be operated upon." It is important to remember that patients with acute fulminating ulcerative colitis do not often die as a result of operation, but as a result of disease. Even extensive operations are tolerated well, provided the disease is eradicated. The colon, severely diseased with ulcerative colitis, is merely a sac filled with feces, pus, and blood, compared by Crile to "an extensive third degree burn covered with fecal poultice." After colectomy the patient's recovery from the effects of sepsis is often as prompt and dramatic as the recovery which follows cleansing and grafting of a badly infected third degree burn of comparable area. Until the colon is removed, there is a continuous loss of blood and protein into the lumen of the bowel, there is a continuous absorption of the toxic contents of the bowel, and cellulitis, thrombosis, and necrosis of the tissue persist and may be associated with localized areas of peritonitis. Ileostomy does little more than retard the progress of this disease. After ileostomy, fever, toxemia, and bacteremia may continue. Once the colon is removed, the source of these difficulties is eradicated; blood loss is

TABLE I.— AUTHORS' SERIES OF CASES OF ACUTE ULCERATIVE COLITIS WITH DISTENTION

Name and hospital No.	*Age Race Sex*	*Duration of*		*Perforation*	*Distention*	*Cortisone Rx*	*Operation*	*Results*
		Disease	*Acute phase*					
L.K. (13-85-15)	18 WF	1½ mos.	3-day T-100.4 P-152	Yes	Yes	Yes	Total abd. colectomy ileostomy	Good, well at 6 mos.
S.G. (12-83-50)	25 WM	7 yr.	1 day T-104 P-160	Yes	Yes	Yes	Total abd. colectomy ileostomy. Subtotal gastrectomy, drainage of intra-abdominal abscess	Died 3 mos. after operation. Devel. G.I. bleeding and breakdown of anastomosis, leading to abscess
M.S. (02-73-00)	22 WF	1 yr.	1 wk. T-102 P-130	Yes	Yes	No	Colostomy, ileostomy. Total colectomy, abdominoperineal 2 years later	Developed abscess about ileostomy 1 year later
M.S. (03-14-48)	31 WF	5 yr.	5 day T-101.4 P-120	No	Yes	No	Transverse colostomy	Doing well with only few exacerbations 2¾ yr. later
H.C. (07-10-46)	34 CM	1 yr.	3 wk. T-103 P-120	Yes	Yes	Yes	Total abd. colectomy ileostomy, abd. perineal resection 13 days later	Bled massively from rectum, required abd. perineal. Then bled from ileostomy
M.C. (04-03-90)	38 WF	1 yr.	1 wk. T-102 P-130	Yes	Yes	Yes	Ileostomy followed in 1 mon. by total abd. colectomy	Died 3 days postop. Septicemia. Abscess in heart and kidneys subdiaphragmatic abscess
H.J. (01-10-00)	27 WF	4 mos.	4 day T-103 P-108	No	Yes	No	Subtotal colectomy ileostomy, abd. perineal resection 2 yrs. later	Devel. intestinal obstruction (small bowel) due to adhesions after 1st oper. relieved by oper. Did well otherwise
M.L. (01-79-09)	40 WF	5 yr.	3 wk. T-102 P-96 1 day perforation	Yes	Yes	Yes	Subtotal colectomy ileostomy. Abd. perineal 2½ yr. later	O.K. after first oper. Died after second perforation
K.L. (08-84-75)	31 CM	2 wk.	2 wk. T-103 P-120	Yes	Yes	Yes	Total abd. colectomy ileostomy. Abd. perineal 15 mos. later	Did well. Abd. perineal for bleeding from rectum

checked; fever and toxemia subside; serum proteins rise rapidly; evidence of vitamin deficiency disappears; cutaneous ulcerations heal; and arthritis subsides. All of these results tend to occur with dramatic suddenness after colectomy, whereas after ileostomy alone their occurrence may be so slow that measurement must be in weeks or months instead of in days. Finally, the potential danger of perforation, ever present in the enormously distended colon, is eliminated by the removal of the dilated segment.

ANALYSIS OF THE PRESENT SERIES

The 9 patients treated at the University of Pennsylvania for acute fulminating ulcerative colitis with abdominal distention were essentially young individuals averaging just under 30 years of age. There were 6 females and 3 males, which is not surprising in that in many series a somewhat higher incidence was reported in females. Seven of our patients were white and 2 were colored, which is in keeping with the general admission statistics at the Hospital of the University of Pennsylvania. With the exception of 1 patient who had had a history of ulcerative colitis for 7 years and 2 others whose history had begun 5 years prior to admission, the patients, on careful questioning, were believed to have had the disease for less than 1 year prior to the time of operation. In 3 cases, the disease had been present for 4 months or less.

The acute phase of the disease had been present for 1 week or less in two-thirds of the patients, with the longest interval between the acute phase and surgical intervention being 3 weeks. In 7 of the 9 patients the colon had already perforated at the time of surgical intervention, and in all marked distention was demonstrated by physical examination and x-ray studies.

Each of the patients received a trial of intensive medical therapy; 6 of the 9 were given steroid medication prior to the decision for operation. In none of the cases did steroids alter the pathologic progress.

The operative treatment in 6 patients consisted of an immediate subtotal or total colectomy and the establishment of an ileostomy. All of these patients survived the initial postoperative period without difficulty. In 1 patient the procedure was limited to a transverse colostomy primarily because the woman was in her sixth month of pregnancy and it was considered unwise to carry out a colectomy for fear of interruption of the pregnancy and excessive bleeding from the engorged pelvic veins (Fig. 3). One additional patient was treated by ileostomy alone and the postoperative course was so poor that abdominal colectomy was necessary within 1 month (Case 2). In the final patient decompression was accomplished by colostomy, and an ileostomy was established. She required colectomy at a later date because of abscess formation within the peritoneal cavity. In all of these patients progress was good as far as the underlying disease process was concerned, with the exception of the patient who had ileostomy alone. One patient with colectomy and ileostomy succumbed to massive gastrointestinal bleeding from a duodenal ulcer, and a second expired after an abdominoperioneal resection of the rectal stump 2½ years after the initial subtotal colectomy. The 1 patient treated by transverse colostomy has had several exacerbations of the disease, but each time refused operative intervention. She is being followed up in our gastrointestinal clinic and has exhibited no further evidence of an acute fulminating process. Her colostomy is still functioning.

FIG. 3. Roentgenogram of abdomen of patient M. S. demonstrating marked distention particularly limited to the transverse colon. This patient underwent transverse colostomy for fear of interruption of her pregnancy.

CASE REPORTS

Two cases from our series are presented below to illustrate our current approach to the treatment of acute fulminating ulcerative colitis with distention.

CASE 1. L. K. was an 18 year old single white female who was well until approximately 6 weeks prior to her admission to this hospital. At that time she manifested bloody diarrhea and progressive weight loss. She was admitted to another hospital at which time the diagnosis of ulcerative colitis was established by proctoscopy and barium enema examination. The patient was placed on a rather intensive program of antibiotics and steroid therapy with little improvement of her condition. Diarrhea became more severe, and approximately 10 days prior to her transfer to this hospital daily elevations of temperature to 103 degrees and marked tachycardia developed. She noted crampy abdominal pain and abdominal distention. The dosage of steroid medication was increased to very high levels and additional antibiotics were given, but the patient's condition deteriorated

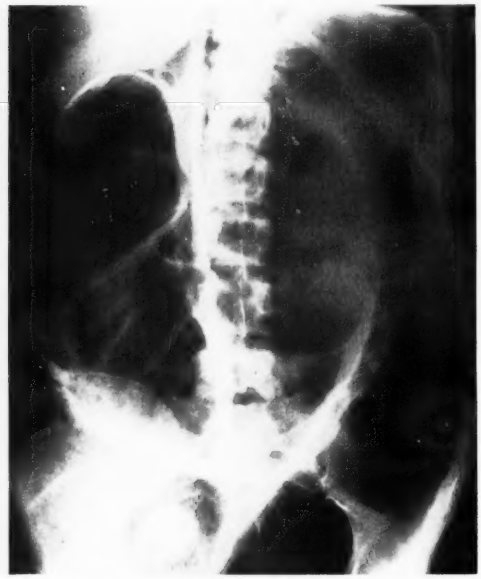

FIG. 4. Roentgenogram of abdomen of patient L. K., demonstrating extreme distention of the colon.

rapidly. She was transferred to the Hospital of the University of Pennsylvania, where, on admission her blood pressure was 110/70, her temperature was 100.4 degrees rectally, and her pulse rate was 152 per minute. The only positive physical finding was a greatly distended, and relatively silent, tender abdomen. Laboratory studies revealed a hemoglobin of 9 grams per cent, a leucocyte count of 11,900, and serum electrolytes essentially within normal limits. Our clinical impression was that perforation of the colon had already occurred and this conclusion was substantiated by survey films of the abdomen (Fig. 4).

TABLE II.—REVIEW OF MORTALITY WITH VARIED TREATMENT IN ACUTE FULMINATING ULCERATIVE COLITIS

Author	*Date*	*Medical therapy, per cent*	*Ileostomy alone, per cent*	*Ileostomy and colectomy (one stage), per cent*
Crile	1951	73	63	14
Gardner	1951	—	100	5.8
Ripstein (11)	1954	—	60	9
Brooke	1956	—	16.6	29
Schroeder	1956	—	57	0
Lumb	1956	0	—	66
McConnell	1958	38	0	9
Peskin and Davis	1959	0	0	14.3
Over-all mortality		57 (16 of 28)	50 (16 of 32)	15.9 (11 of 69)

The roentgenograms revealed a large bowel greatly distended from cecum to sigmoid colon with obvious free air under each hemidiaphragm (Fig. 5). It was believed that immediate surgical intervention offered this girl her only chance of survival, and after transfusion with whole blood and administration of additional steroid medication, the patient was taken to the operating room, approximately 4 hours after admission. At operation under general endotracheal anesthesia, the colon was greatly dilated and a site of perforation was found in the sigmoid colon. It was thought that subtotal colectomy should be performed, and this was carried out, establishing an ileostomy and mucous sigmoid colostomy. The patient tolerated the operative procedure well and had an uneventful postoperative course. She was discharged from the hospital, having gained 9 pounds and having adapted well to the ileostomy. Follow-up examination some 6 months after operation revealed an additional weight gain and no symptoms referable to the gastrointestinal tract.

CASE 2. M. C., a 38 year old, single, white female, was well until approximately 1 year prior to admission to the Hospital of the University of Pennsylvania. At that time she noted intermittent periods of bloody diarrhea, and the diagnosis of ulcerative colitis was established by proctoscopic examination. The disease was mild and the patient was able to work as a clerk between the episodes of bloody diarrhea.

One week prior to admission marked diarrhea developed which became grossly bloody on the day before admission. She experienced abdominal cramping and distention and a temperature elevation to 102 degrees. Her condition deteriorated rapidly and she was hospitalized. On physical examination her temperature was 102 degrees, her pulse rate was 130 per minute, and her blood pressure was 120/80. The patient appeared acutely ill with a distended abdomen and minimal peristalsis. There was marked tenderness on palpation of the left lower quadrant of the abdomen. The rectum contained bloody stool. Laboratory studies revealed a hemoglobin of 9.8 grams per cent, and leucocyte count of 8,800.

X-ray examination of the abdomen demonstrated a markedly distended large bowel down to the sigmoid colon. No free air was seen. Despite an intensive medical program including blood and electrolyte replacement, antibiotic therapy, and intestinal intubation, the patient's condition continued to deteriorate. She was taken to the operating room 48 hours after admission to the hospital, and on exploration the entire colon was found to be edematous and thickened with areas of walled-off perforation in the sigmoid region. An ileostomy was performed. The patient did well immediately after operation, but again diarrhea developed with skin excoriation around the ileostomy stoma. Bloody discharge from the rectum increased and the patient became toxic. Hemolytic staphylococcus aureus was cultured from the blood stream and

bilateral pleural effusion developed. The rectal discharge increased and reached 700 cubic centimeters a day and the abdominal distention became marked. It was believed that the patient's condition was desperate, but that colectomy offered her the one chance for survival. At operation (1 month after ileostomy), the colon was dilated, thinned, and very friable. There were numerous intra-abdominal abscesses. An abdominal colectomy was performed but the patient died on the second postoperative day. It is our opinion that had a colectomy been performed at the initial operation the outcome might well have been different.

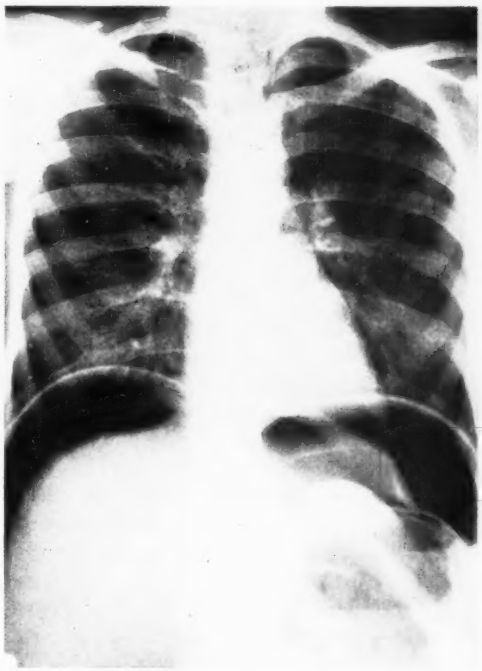

FIG. 5. Roentgenogram of chest of patient L. K., revealing obvious free air under each hemidiaphragm.

DISCUSSION

It is evident from a review of the literature that controversy still exists concerning the therapy of acute fulminating ulcerative colitis. Because of the remarkably few cases in which the phenomenon of marked colonic distention is exhibited in association with acute colitis, even less of a critical analysis is possible in these instances (Table II).

Cattell and Colcock have championed the conservative approach to this problem. In reviewing their cases, they found a lower mortality rate with ileostomy than with simultaneous ileostomy and colectomy. They believed that the extremely toxic patient had a better chance for recovery if an ileostomy alone was established because of the higher mortality rate of colectomy and ileostomy and, because, once the patient tolerated the ileostomy he regained his weight and strength so that colectomy could then be carried out 2 or 3 months later on a good risk individual with a well functioning ileostomy. They further stated that in the patients in whom perforation of the colon has already taken place at the time of operation, "little further can be done except to treat them for generalized peritonitis. An ileostomy should then be done as soon as their general condition permits. Any residual peritoneal abscesses should be drained."

The middle ground has been held by Brooke (2, 3) who reported on 13 patients, 6 treated by ileostomy alone with a mortality rate of 17 per cent (1 of 6) and 7 treated by simultaneous ileostomy and colectomy with a mortality rate of 29 per cent (2 of 7). Perforation had occurred in 6 of the patients in the latter group, and 2 of them died. Brooke believed that the risk of operation was about equal in the two procedures but that convalescence was much slower after ileostomy alone. He further stated "though I prefer to undertake primary colectomy if possible, there are occasions when ileostomy alone is all the patient can sustain."

Many recent reports have substantiated the good results which can be achieved with the more radical approach of combined ileostomy and colectomy. Ripstein (10–12), Crile, Schroeder, Gardner, and Ferguson have written of a lower mortality and morbidity with colectomy in acute ulcerative colitis. Numerous instances of patients treated by ileostomy alone are cited. In many of these cases, emergency colectomy was necessary because of the rapid deterioration of the patient. They point out that a good number of these individuals could have been salvaged by primary colectomy.

In only 1 series in the literature are the hazards of acute colitis with large bowel distention clearly established and an attempt is made to define adequate therapy. Of the 26 patients of McConnell and associates, 13 were treated by conservative medical management with 5 deaths (38 per cent), 2 were subjected to ileostomy alone with no deaths (0 per cent), and 11 had ileostomy and colectomy with 1 death (9 per cent). From this series as well as our own, it can be concluded that: (1) medical therapy has very little if any place in this syndrome of acute fulminating colitis with distention, and (2) colectomy with ileostomy as a primary procedure is safe and provides the patient with the relief necessary to insure against continued morbidity from the disease process.

The over-all mortality for patients with acute fulminating ulcerative colitis treated by the 3 methods, as shown in Table II, is medical 57 per cent, ileostomy alone 50 per cent, ileostomy and colectomy 15.9 per cent. These figures, although selective to a degree, should serve to stimulate a more radical approach to these patients at an early period in their disease process.

SUMMARY

1. The syndrome of acute fulminating ulcerative colitis is defined and its pathologic physiology discussed, particularly in respect to the marked distention of the colon which may complicate the evaluation of the patient. Emphasis is placed on the physical examination of the abdomen and the roentgen findings in diagnosis.

2. The literature is reviewed and the various types of therapy are evaluated.

3. A rationale for present day surgical treatment is presented.

4. The authors' series of 9 cases is analyzed. The failure of prolonged medical management and the lasting good results achieved with simultaneous ileostomy and subtotal colectomy are stressed.

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HUMAN CARTILAGE STORED IN PLASMA

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IN A PREVIOUS ARTICLE (1) a study was outlined to determine the success of human cartilage as a homograft. This problem was approached by examining cartilage stored in various media which were designed to maintain the cartilage or to kill it. The general characteristics of fresh living human costal cartilage were reported upon in the first article (1). Then, in the second article (2), the storage of cartilage in merthiolate-saline was shown to result in rapid death of the cartilage and marked electrolyte exchanges between this tissue and both its storage and transplantation media. The scope of the present article is limited to the study of cartilage stored in plasma and later transplanted into human volunteers.

METHODS

The methods of preparation and the examination of cartilage have already been described (1, 2). The cartilage was placed in sterile bottles containing plasma, capped, and refrigerated at 3 to 5 degrees C. Approximately 7 cubic centimeters of plasma were used for each gram of cartilage. The plasma was obtained from the blood bank 21 days after donation. Two-hundred units of penicillin and 200 micrograms of streptomycin per cubic centimeter were added. The plasma was selected as a storage medium to approximate the internal environment of living cartilage in the human body and thus allow preservation of viability for a limited period of time. One inch blocks of cartilage which had been stored in plasma for varying periods of time were transplanted subcutaneously into the abdominal wall of human volunteers and later removed for examination.

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This investigation was supported by a grant from the Office of Naval Research, U. S. Navy.

RESULTS OF CARTILAGE STORED IN PLASMA

Supravital stains. Sixty-eight cartilage specimens taken from 17 cadavers were examined. Cellular viability decreased progressively over a period of 40 days, with no viable cartilage remaining at the end of 50 days (Fig. 1). In the first week, the majority of the cells which appeared nonviable were in the peripheral 1 millimeter of the cartilage block. In ensuing weeks, there were increasing numbers of nonviable cells scattered throughout the cartilage block. An abrupt decline in viability occurred between 25 and 35 days of storage.

Metabolic studies. Seventy-eight determinations were made on plasma-stored cartilage from 15 cadavers. The anaerobic glycolysis ($Q_G^{N_2}$) of the cartilage decreased to zero after about 45 days (Fig. 1). Thereafter, the cartilage appeared to bind carbon dioxide in increasing amounts, resulting in a negative $Q_G^{N_2}$. With increasing lengths of storage, the $Q_G^{N_2}$ became increasingly negative until, at the end of 100 days of storage, it reached a value which is about 270 per cent below the fresh value. Following this, a marked rise of $Q_G^{N_2}$ occurred which was probably due to bacterial contamination.

Histologic studies. Six pieces of cartilage stored for periods varying from 184 to 216 days were examined. All pieces showed evidence of extensive degeneration and, in a few cases, bacterial growth.

Electrolyte and water exchange. Thirty-four analyses each of sodium, potassium, and water content were made on cartilage from 16 cadavers within 2 months of storage. As compared with control values obtained by analyses of fresh cartilage, the sodium con-

TABLE I.—SALT AND WATER SHIFTS IN HUMAN COSTAL CARTILAGE AFTER STORAGE IN PLASMA SOLUTION

Condition of cartilage	*No. of determinations*	*Days stored*	*Days transplanted*	*Na mEq./kgm.*	*K mEq./kgm.*	*Per cent H_2O*	*I Na* mEq./L.*	*I K† mEq./L.*
Fresh	64	—	—	172.46	20.3	60.8	—	—
Stored	17	60	—	118.52	29.2	61.9	133.20	11.40
Stored and transplanted	7	19	549	216.75	7.44	69.2	—	—

*I Na = Sodium concentration of the storage medium.
†I K = Potassium concentration of the storage medium.

TABLE II.—CALCULATED VALUES OF SALT AND WATER SHIFTS WITHIN COSTAL CARTILAGE

Condition of cartilage	*Days stored*	*Days transplanted*	*Int.* c.c./kgm.*	*Ext.† c.c./kgm.*	*△Na mEq./kgm.*	*△K mEq./kgm.*	*△Int.‡ c.c./kgm.*	*△Ext. c.c./kgm.*
Fresh	—	—	145.00	463.00	—	—	—	—
Stored	60	—	(145.00)	474.00	−53.94	+8.9	(0.0)	+11.00
Stored and transplanted	19	549	53.00	638.90	+98.23	−21.80	−91.90	+164.00

*Int. = Intracellular water volume.
†Ext. = Extracellular water volume
‡△ = Change of quantity measured.

TABLE III.—TRANSPLANTED CARTILAGE (PLASMA-STORED)

Age in years		*Days*		*Per cent*		*Per cent*	*Per cent*	*Per cent*	*Per cent*	*Total*	*Central*
Donor	*Recipient*	*Stored*	*Transplanted*	*viable*	$Q_G^{N_2}$	*normal*	*pyknotic*	*karyolytic*	*"dropped-out"*	*area**	*fibrous tissue**
39	29	26	134	30	+0.003	7	10	56.5	26.5	128.22	.4280
6	48	28	163	95	+0.072	38.5	38	14.5	8	212.48	2.302
6	24	18	172	0	0.000	0	0	96	4	19.59	0
6	42	7	174	2.5	+0.194	59	24	10	7	51.14	.1187
39	23	34	447	15	—	24	24	35	28	144.77	.7987
24	20	18	453	40	+0.078	13	10	68	9	93.61	0
6	16	18	471	0.5	+0.076	6	5	79	10	70.25	.3875
43	40	14	983	45	+0.061	9	17	51	22	91.90	0
6	40	12	939	80	+0.049	0	20.5	48	31.5	196.05	1.291
6	3	26	1039	2.5	+0.127	15	10	70	5	55.58	0
36	9	6	1059	50	+0.040	24	10	60	6	152.86	1.810
						Average values:					
20	29	19	549	32.8	+0.070	17.7	14.3	53.7	14.3	110.59	.6487

* = $Cm.^3$
Per cent total central fibrous tissue .59

tent decreased by 32 per cent, the potassium content increased by 44 per cent, while there was a negligible change of water content (Table I). Values derived by methods previously described (1) revealed changes of intracellular and extracellular water volume (Table II).

RESULTS OF TRANSPLANTED CARTILAGE PREVIOUSLY STORED IN PLASMA

Supravital stains. Examinations were made of 14 pieces of plasma-stored cartilage which had been transplanted into 11 patients for 134 to 1,059 days. The degree of survival was variable, averaging 33 per cent viability (Table III). The viability of the transplanted cartilage appeared to be independent of the duration of storage or transplantation.

Metabolic studies. Studies of anaerobic glycolysis were made on 14 pieces of cartilage which had been transplanted into 10 patients for 134 to 1,059 days. The mean $Q_G^{N_2}$ was found to be +0.070 (Table III). This value is about 40 per cent higher than that for fresh cartilage.

Histologic studies. Histologic examinations were made on 19 pieces of cartilage which had been transplanted into 11 human volunteers for 134 to 1,059 days. There was an average of 17.7 per cent normal cells, 14.3 per cent pyknotic, 53.7 per cent karyolytic, and 14.3 per cent "dropped-out." Central fibrous tissue invasion by the

host, represented as per cent of total cross sectional area, averaged 0.59 per cent (Table III). Infiltration by lymphocytes and macrophages was minimal.

Electrolyte and water exchange. Seven analyses each of sodium, potassium, and water content were made on plasma-stored cartilage which had been transplanted into human volunteers for 983 to 1,059 days (Table I). Compared with values obtained from plasma-stored cartilage (stored an average of 60 days), the sodium content increased about 83 per cent, the water content increased about 12 per cent, and the potassium content decreased about 75 per cent (Table II). Since the transplanted cartilage was stored in plasma for an average of only 19 days prior to transplantation, the magnitude of the shifts would be less although the direction of the shifts would remain the same.

DISCUSSION

Cartilage stored in human plasma became nonviable after 40 to 60 days of storage. In this study the rate of anaerobic glycolysis appeared to be a function of at least two factors. The first was a loss of viability during the storage period. The second, an unknown factor, eventually produced a negative $Q_G^{N_2}$ value. This negative value may be accounted for by the loss of base which occurred during storage.

Analyses of electrolyte shifts were made at the end of 60 days of storage or just after the $Q_G^{N_2}$ of the plasma-stored cartilage became negative. These analyses revealed a gain of potassium during storage resulting from equilibration of the cartilage with the high potassium content of the plasma storage medium (Table I). The shift of sodium during storage appeared to be due to two factors. First, the gain of storage medium water (Table II) would account for an uptake of about 1.5 milliequivalents of sodium per kilogram of tissue. Second, since the cartilage exhibited a net loss of 53.9 milliequivalents of sodium per kilogram of tissue (Table II) a loss of about 55.4 milliequivalents from the bound sodium must have occurred. Thus, if sodium and potassium were the major cations which shifted, there occurred a loss of base binding capacity equivalent to about 45 milliequivalents per kilogram of tissue.

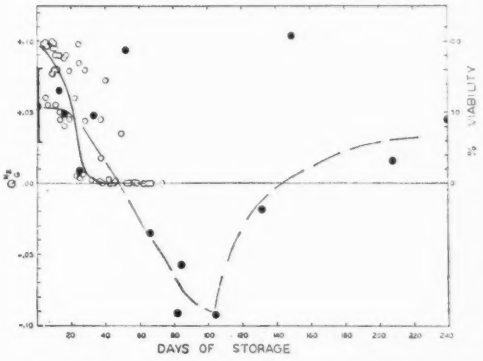

FIG. 1. The effect of storage in human plasma on the anaerobic glycolysis and the viability of human costal cartilage. Viability as determined by supravital staining (○); anaerobic glycolysis (●).

Normally, during the measurement of anaerobic glycolysis, the acid metabolites produced by the tissue in the absence of oxygen liberate carbon dioxide from the Krebs-bicarbonate bathing fluid in the Warburg flask. This loss of carbon dioxide is used as the measure of anaerobic glycolysis, normally indicated by a plus sign in front of the actual numerical value. Since loss of base by the tissue during measurement of anaerobic glycolysis would produce an apparent gain of carbon dioxide by the tissue in a 1 to 1 relationship, the measured loss of base after 60 days of storage would give an apparent gain of 1.008 millimeters of carbon dioxide gas per milligram of cartilage tissue. This figure is 10 times more than sufficient to account for the $Q_G^{N_2}$ value (-0.092) measured. Actually, these values are of the same order of magnitude since the anaerobic glycolysis determinations were made over a 1 hour period after 60 days of storage time, while the loss of base occurs during a 60 day period. Furthermore, this loss probably does not occur in a linear fashion with respect to storage.

Thus, during storage, cartilage became

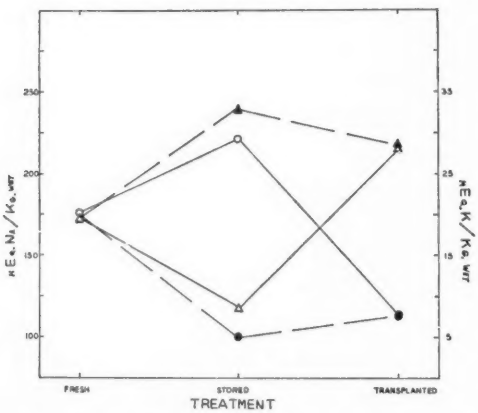

FIG. 2. The electrolyte pattern of merthiolate and plasma stored and transplanted human costal cartilage. Sodium (▲) and potassium (●) shifts in merthiolate-stored cartilage; sodium (△) and potassium (○) shifts in plasma-stored cartilage.

nonviable after 40 to 60 days, and exhibited a loss of sodium amounting to about 55 per cent of the total bound sodium of the extracellular space (1). The curious negative $Q_0^{N_2}$ value observed after 60 days of storage may well be accounted for by the loss of base binding capacity.

After an average of 549 days of transplantation, the plasma-stored cartilage was less than 25 per cent viable, the actual figure differing somewhat with the method used for determination. Supravital staining indicated that 33 per cent of the cells were viable, while the histologic studies indicated that 18 per cent of the cells appeared normal (Table III). The anaerobic glycolysis further suggests that a small but definite number of cells remain viable based upon the following considerations: the $Q_0^{N_2}$ of plasma-stored transplanted cartilage (+0.070) was the same as that for merthiolate-stored transplanted cartilage (+0.069). The merthiolate-stored transplanted cartilage was known to be dead at the time of transplantation, and, therefore, the anaerobic glycolysis was presumably due to the invading fibrous tissue. Since plasma-stored transplanted cartilage exhibited less invasion, part of the $Q_0^{N_2}$ displayed must be due to the presence of viable chondrocytes. The fact that both merthiolate-stored transplanted cartilage and plasma-stored transplanted cartilage exhibited an anaerobic glycolysis greater than that for fresh cartilage is explained by the presence of invading tissue with a high rate of metabolism.

The results of the electrolyte and water studies further substantiate the view that only a small proportion of the chondrocytes are viable after transplantation. The loss of potassium exhibited by the plasma-stored transplanted cartilage is due to: (a) transplantation of the cartilage from the storage medium, containing a high potassium concentration, into the host, presumably containing a normal potassium concentration; (b) death of the cells during transplantation. The sodium gain is due to three distinct mechanisms. First, when the chondrocytes disintegrate, their intracellular water volume becomes a part of the extracellular water volume. Since the intracellular space contains no sodium this conversion would account for a gain of 14.2 milliequivalents of sodium per kilogram of tissue. Second, the gain of 72 cubic centimeters of water per kilogram of tissue would account for an uptake of 10.5 milliequivalents of sodium per kilogram. Third, since the total sodium gain exceeds the combined gain of the first two mechanisms, the remainder (74.5 mEq./kgm.) must be an increase in the bound sodium.

Although the electrolyte pattern of merthiolate-stored cartilage (2) is markedly different from that of plasma-stored cartilage (Table I), the final values after transplantation are essentially the same. The difference of the potassium contents during storage is due to the difference of time of chondrocyte death of the two types of cartilage. After transplantation all of the merthiolate-stored chondrocytes were dead, while the surviving 25 per cent of the plasma-stored chondrocytes may have been damaged, resulting in a loss of intracellular potassium.

Most of the sodium exchanges exhibited in these studies are of the bound sodium

fraction. Since the base-binding materials of cartilage are the chondroitin sulfate-protein complexes, their binding capacity may be modified by the *p*H of the storage medium. The *p*H of the plasma storage medium decreased progressively during the first 2 weeks, thus depressing cation binding by reducing the negative charge of the proteins. The merthiolate storage medium, with a *p*H of about 8, would enhance cation binding. This may well account for the differences of sodium binding observed in the two storage media. After transplantation, the amount of bound sodium is the same in both the merthiolate-stored and plasma-stored cartilage, presumably since both are subject to the same environmental *p*H, that of the host.

The viability of cartilage decreased during transplantation from 55 per cent (i.e., after 19 days of storage) to about 25 per cent after an average of 549 days of transplantation. However, this does not necessarily indicate that transplantation leads to chondrocyte death since these cells may have been irreparably damaged during storage. All of the chondrocytes would have been nonviable after just 50 days of storage.

Central fibrous tissue invasion in plasma-stored transplanted cartilage was 0.59 per cent of the total cross sectional area. Since fresh cartilage exhibited 0.093 per cent "fibrous tissue" areas (1), the final adjusted value for percentage of fibrous tissue invasion of total cross sectional area would be approximately 0.5 per cent.

In this study, fibrous tissue invasion was unrelated to either duration of storage or the duration of transplantation. Even though the amount of viability present in plasma-stored cartilage after transplantation was not great, there was a measurable correlation between the viability and fibrous tissue invasion of plasma-stored transplanted cartilage and merthiolate-stored transplanted cartilage. Thus, plasma-stored transplanted cartilage which exhibited a viability approximately 25 per cent of fresh cartilage displayed a degree of fibrous tissue invasion of only ⅔ that of merthiolate-stored transplanted cartilage, which contained no viable chondrocytes. It would appear, therefore, that fibrous tissue invasion is inversely related to the degree of viability of cartilage transplants. Fibrous tissue invasion probably occurs extensively in the peripheral zone of nonviable cells, but this could not be quantitatively measured in this study. Since invasion will originate peripherally in any case and the preparation of the cartilage block itself results in necrosis of the peripheral chondrocytes, the determination of the relationship of these two phenomena in such a short term study is difficult.

SUMMARY

When cartilage was stored in plasma it exhibited a decreasing viability, reaching 0 per cent at about 50 days. A noticeable loss of sodium during storage was possibly due to the acidity of the storage medium. A slight gain of potassium occurred during storage, probably due to the excess potassium in the storage medium.

The viability of the cartilage after transplantation was approximately 25 per cent, which is less than that of the average at the time of transplantation. The decrease in viability during transplantation may have been caused by injury to the cell during storage or by some direct action by the host tissue, the former appearing to be the more significant factor. The sodium lost during storage was approximately regained during transplantation, while a marked loss of potassium occurred during transplantation. The degree of host fibrous tissue invasion correlates with neither the duration of storage nor the duration of transplantation, but appears to be inversely related to the degree of viability.

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METABOLIC RESPONSE TO CRANIOCEREBRAL TRAUMA

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THE PRESENT STUDIES were undertaken in an attempt to establish a rational basis for posttraumatic nutritional support of neurosurgical patients who had sustained craniocerebral trauma. In the past, rather widely varying recommendations have been made regarding the proper support of such patients. During recent years valuable contributions have been made to our understanding of metabolic deviations following bodily trauma, mainly through balance studies, and it seemed logical to apply the technique to patients with head injury.

METHODS

During the past 3 years, 11 patients have been studied (Table I). Selection has been made from all patients admitted to the neurosurgical service at Cincinnati General Hospital and has been based on: (1) presence of moderately or markedly severe brain injury, (2) minimum or absence of associated bodily injury, and (3) absence of any known pre-existing metabolic disturbance. The balance study has been started immediately after deciding that the patient was a suitable candidate, usually within 2 to 3 hours after injury. Although no record was obtainable of intake prior to injury, there was in no instance any posttraumatic intake prior to beginning the metabolic study. Data were not utilized from patients who died soon after admission or in whom complications developed increasing the error of a balance procedure, such as vomiting or diarrhea.

Catheter drainage was instituted immediately and maintained throughout the period of observation which lasted from 5 to 15 days. Blood samples for chemical determinations were drawn, and the patient's weight recorded, at the beginning of the study and periodically thereafter.

Standard balance methods were used. Urine was collected in 24 hour aliquots. No analysis was made of stools. It is recognized that this practice introduced a small error into the cumulative balance, but since the stools were consistently small and infrequent, the metabolic balance trends were not distorted in a short term study. Moreover, there is evidence that fecal nitrogen, sodium, and potassium are unrelated to dietary intake and vary within a narrow range.

Accurate records were kept of all intake. During the first few days this consisted of intravenous solutions which varied somewhat during the study. Later, after danger of vomiting was over, feeding was done by nasogastric tube. Aliquots of the feeding mixture were saved and later pooled at the end of each study; the pooled material was analyzed for sodium, potassium, and nitrogen. Analyses for sodium and potassium were done by flame spectrophotometry and nitrogen determinations by the micro-Kjeldahl method.

The method of charting followed that used by Moore and Ball (6) for presenting balance study data. A typical record of a moderately severe injury is demonstrated in Figure 1.

RESULTS

Nitrogen. The most consistent metabolic effect noted was a nitrogen loss which was often quite large and seemed to be unrelated to nitrogen intake within certain limits. The

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negative balance was usually in the range of 10 grams per day, corresponding to a loss of approximately 300 grams of muscle tissue daily.

The possible role of associated trauma was investigated by comparison of the balance in those patients who had fracture of long bones in addition to head injury with those who had only craniocerebral trauma. There were 3 patients with fractures of bones (Table I) and these had an average net loss of 11 grams of nitrogen daily. This was very slightly greater than those with comparable degrees of head injury alone, and it appears, therefore, that the nitrogen loss is directly attributable to the head injury.

Attempts to correlate nitrogen loss with severity of injury were difficult because of the problem of classification of cerebral injury as to severity. There was very little correlation if the patient's initial condition was used as a basis for grading. When patients were graded on the basis of length of hospitalization due to injury (all patients studied have survived) there was a definite correlation (Table II). Patients with meningeal hematomas removed early showed less disturbance of nitrogen metabolism than those whose main injury was cerebral contusion or prolonged compression due to unrecognized hematoma. There was no correlation with the site of maximum brain injury.

In 2 patients there was evidence that intracranial surgery for removal of hematoma and amputation of a contused temporal lobe precipitated a decline of nitrogen loss. This observation may be interpreted as indicating that the surgical procedure caused a diminution of the "stress" response.

Nitrogen feeding during the period of posttraumatic catabolism was not accompanied by significant decrease of negative balance. In 2 patients nitrogen intake was begun during the period of marked negative balance and there was evidence from the balance data that only a small portion of the intake was utilized while the remaining amount was excreted. The nonutilized amount of nitrogen was excreted in the urine (Fig. 2).

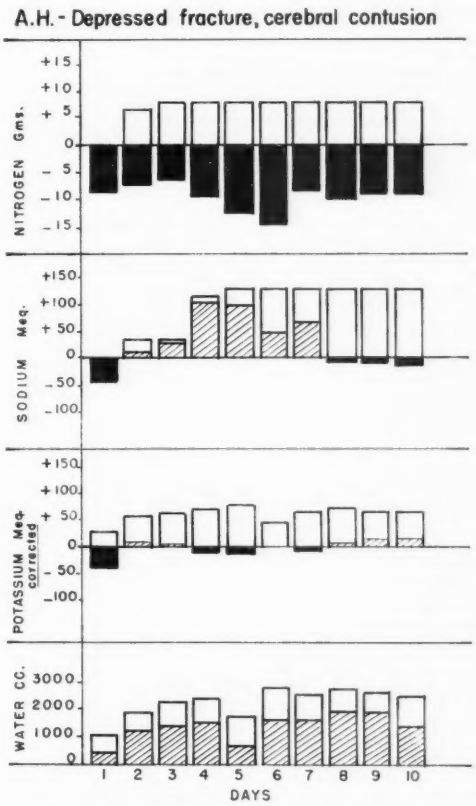

FIG. 1. Typical balance study. Intake is charted upward from the zero line; output is charted downward from the top of the intake line. The resulting positive or negative balance is shown as a shaded area above the zero line or a solid area below the line. This study demonstrated: (1) moderately large negative nitrogen balance despite nitrogen intake, (2) early sodium retention followed by equilibrium, (3) potassium equilibrium, after correction for potassium release by protein catabolism, and (4) positive water balance throughout – insensible loss not calculated.

Our studies suggest that nitrogen loss may be modified by caloric intake. In contrast to the starving person whose protein catabolism is significantly reduced by a relatively small caloric intake, the data suggest that intake must exceed 1,000 calories to achieve a reduction of nitrogen loss.

In summary, the following conclusions may be drawn concerning nitrogen metabo-

TABLE I

Patient	*Age, yrs.*	*Type of injury*	*Severity (1–4+)*	*Length of hospitalization, days*	*Associate injuries*
P.R.	19	Contusion	3+	14	0
J.H.	40	Epidural hematoma Contusion	3+	16	0
R.D.	20	Subdural hematoma Contusion	3+	18	0
G.J.	34	Epidural hematoma Contusion	4+	150+	0
J.R.	45	Gunshot wound	3+	30+	0
W.B.	31	Subdural hematoma Contusion	3+	17	0
A.H.	21	Depressed fracture Contusion	3+	25	0
L.B.	28	Subdural hematoma Contusion	3+	16	0
L.M.	30	Epidural and subdural hematomas Contusion	4+	27	Fracture: clavicle and ribs
L.C.	28	Basal fracture Contusion	2+	29	Fracture: mandible and forearm
E.W.	36	Subdural hematoma Contusion	4+	44	Fracture: clavicle and ribs

lism: (1) there is in most instances a relatively large protein catabolism lasting for at least 10 days and unrelated to associated bodily trauma, (2) the severity of nitrogen loss seems to be related to the extent and type of injury but not to the location of cerebral tissue damage, (3) feeding of nitrogen during the posttraumatic period has very little effect on the degree of negative balance, and (4) increased caloric intake may have a protein-sparing effect when supplied in excess of 1,000 calories daily.

Sodium. The anticipated response of sodium metabolism was one of rather marked retention during the posttraumatic period. Although sodium retention did occur it was quite variable in degree and duration in contrast to the effect on nitrogen metabolism. The initial retention of sodium in most patients was not as great as has been noted after major abdominal surgery. Retention usually lasted only from 2 to 3 days, and in all patients in whom the study continued for 10 days sodium equilibrium was restored.

TABLE II

Patient	*Hospitalization, days*	*Average daily N-loss, grams (corrected to 70 kgm. person)*
P.R.	14	3.8
J.H.	16	7.5
L.B.	16	1.5
W.B.	17	7.3
R.D.	18	9.7
A.H.	25	9.3
L.M.	27	10.6
L.C.	29	12.0
J.R.	30+	13.9
E.W.	44	10.3
G.J.	150+	14.5

There was a tendency toward prolonged sodium retention in the patients with more severe cerebral injury. When it occurred the urine concentration of sodium was quite low. In 3 patients this amounted to a retention of approximately 140 milliequivalents daily (nearly 1 liter of physiologic saline) lasting for from 5 to 6 days. While our patients were generally young, previously healthy, and presumably without pre-existing metabolic disturbances, it seems reasonable to expect that older individuals with decreased cardiac reserve would not tolerate such retention of salt.

We have been unable to correlate sodium

balance with the location of cerebral damage. Areas which have been previously implicated are the inferior frontal lobe and the hypothalamus. It is, of course, impossible to delineate the extent of trauma in patients who survived but there was no greater retention in those patients with known frontal lobe damage.

It is of interest that the 2 patients who exhibited an improved nitrogen metabolism after surgery also showed a sudden decline of sodium retention simultaneously. Again, the suggestion is that the stress reaction has been suddenly relieved by decompression of the injured brain.

Plasma sodium levels were determined approximately every 3 days during the studies. The expected lowering of plasma sodium was noted despite the rather marked retention occurring in some patients (Fig. 3). Possible mechanisms for this relative hyponatremia need not be discussed in detail but the principal mechanism is probably dilution by simultaneous retention of water.

No examples of the salt-losing syndrome have been noted. While this condition seems well documented in the literature, it is undoubtedly a rare occurrence.

The following conclusions may be drawn regarding sodium metabolism: (1) sodium retention does exist in most patients for 2 or 3 days followed by a return to equilibrium, (2) the extent of sodium retention is related to the clinical severity of the injury and in certain instances may account for retention of amounts equivalent to 1 liter of 0.9 per cent saline daily for several days, and (3) the normal response of serum sodium to trauma is a decline, and this fact does not signify depletion of body sodium and need for administration of salt unless it falls below 125 to 130 milliequivalents per liter.

Potassium. Potassium metabolism was not significantly affected. There was no period of negative balance to correspond with sodium retention. Plasma potassium levels showed no deviation from normal limits despite the severity of injury and the lack of potassium administration during intravenous feeding. It must be recalled, however, that protein catabolism releases free potassium to the body. Our observations are in agreement with Wise's; he found no aberration of potassium metabolism. This finding is in contrast to the situation encountered in many general surgical conditions in which hypokalemia results from renal and extrarenal potassium loss.

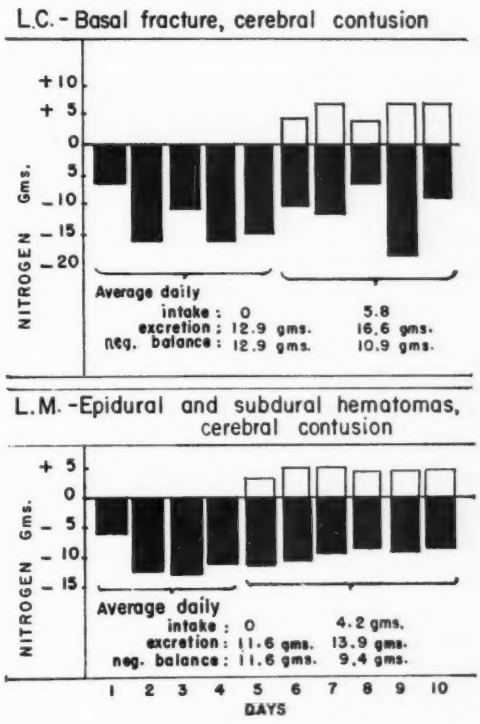

FIG. 2. Nitrogen balance of 2 patients demonstrating characteristic inefficient utilization of administered nitrogen. In patient L. C. the administration of average daily intake of 5.8 grams of nitrogen resulted in an increase of average daily excretion of 3.7 grams. Only 2.1 grams of nitrogen were utilized. Patient L. M. excreted an average of 2.3 grams of 4.2 grams administered.

Water. Water balance is exceedingly difficult to evaluate because of extrarenal losses. Disregarding such losses the cases studied showed a positive balance varying between 430 and 1,480 cubic centimeters daily with an average of 1,100 cubic centimeters. There was no detectable relationship between fever and the apparent positive balance.

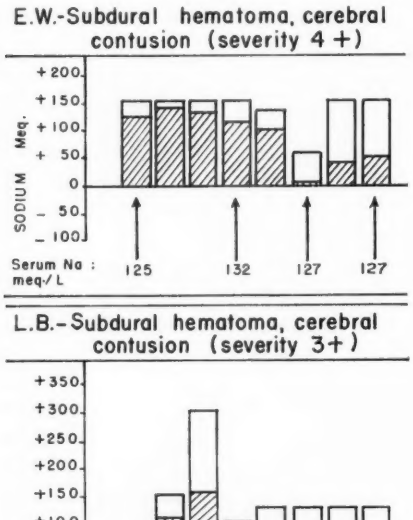

FIG. 3. Sodium balance in 2 patients showing different types of response and lowering of serum sodium despite retention. The degree of retention is apparently related to the severity of injury.

The most commonly observed pattern of water balance was a markedly positive balance on the first day followed by equilibrium or a negative balance and then progressive return toward a positive balance for from 2 to 4 days. There was then a levelling trend but no diuresis. The initial sudden positive balance was usually not accompanied by a simultaneous sodium retention and indeed was associated with small volume of urine with a high concentration of salt. This observation suggests that the initial water retention, as described by LeQuesne, is not due to sodium retention but rather to a sudden release of antidiuretic hormone into the circulation.

With full recognition of hazards of interpreting water balance several conclusions are suggested: (1) there is no strong tendency to water retention; although daily weighings were not made, the largest recorded weight gain was 0.6 kilogram; (2) with the exception of the first day, whatever positive balance occurs is most marked after 3 or 4 days; (3) there is no correlation between salt retention and water balance; and (4) there is no apparent relationship between water balance and severity of injury or location of cerebral damage.

DISCUSSION

There are three specific metabolic disturbances which have special relationships to neurosurgical patients. None has been observed in the group under discussion although the possible aberrations should be considered in applying data of balance studies to practical clinical management of patients.

The first is the so-called cerebral "salt-wasting syndrome" described by Peters, Welt, Sims, Orloff, and Needham. The defect consists of inability to reabsorb sodium chloride despite low sodium and chloride levels in the blood. Balance study of such a patient was performed by Cort who demonstrated no response to adrenal steroids and suggested a direct effect of the central nervous system on renal function. Clinically, there is seen the syndrome of salt depletion with hypotension and azotemia. The patients respond to administration of extra salt but it is essential that the condition be recognized early and treated actively.

The second syndrome which must be distinguished from salt-wasting is water intoxication. This is also characterized by hypotonicity of the body fluids and low plasma sodium and chlorides. The defect, however, is not lack of salt reabsorption but is probably a combination of prolonged and excessive water retention combined with administration of hypotonic solutions. Clinically, the syndrome consists of confusion, drowsiness, coma, and convulsions and may be

mistaken for an expanding intracranial hematoma in the posttraumatic or postoperative period. Dodge, Crawford, and Probst have shown conclusively that the symptoms of water intoxication are due to intracellular edema and not to the lowered extracellular electrolyte concentration. Hypertonic saline to restore normal tonicity of the body fluids is specific therapy.

The third syndrome is characterized by hypernatremia, hyperchloremia, and azotemia. This has been considered by some observers to be a specific neurogenic disturbance resulting from frontal lobe dysfunction. Recent observations by Levitt, Belsky, and Polimeros suggest that the primary defect is a disturbance of antidiuretic hormone release. Many investigators believe, however, that the hypernatremic syndrome actually results from water deprivation due to a combination of loss of normal osmoregulation, increased extrarenal water loss, and impaired consciousness with loss of normal thirst mechanisms. It occurs most commonly in patients receiving tube feedings containing large amounts of solute which must be excreted but inadequate water to cover extrarenal losses and also provide enough for urinary excretion of the solute load. It is estimated that each 1.0 gram of nitrogen requires 40 to 60 milliliters of water for its excretion.

Nutritional support for the head-injured patient should be based on the known metabolic alterations learned from balance studies and should attempt to prevent the excessive metabolic disturbances which have been described. While management of patients with severe derangements of metabolism may be delegated to someone more experienced in handling such problems, avoidance of pitfalls and recognition of impending or actual imbalance are certainly within the responsibility of the neurosurgeon.

Water intake is based on the knowledge that there is no strong retention and that unless fever or tachypnea is pronounced the extrarenal water loss will not be excessive. The appropriate fluid volume to be administered during the first few days is 2,000 to 2,500 cubic centimeters, depending on the size of the patient and environmental temperature. This amount provides 1,000 cubic centimeters for insensible loss and 1,000 to 1,500 cubic centimeters for renal excretion. While urine volume may be low on the first day ("primary water retention" noted previously) a continuing low output without extrarenal losses indicates an excessive water retention which may or may not be accompanied by simultaneous salt retention.

The amount of salt to be used has been the subject of considerable disagreement in the past. Mechanism of cerebral "edema" has apparently been confused with peripheral edema and administration of salt has been severely limited. It is now recognized that water intoxication with increasing cerebral water content is apt to follow use of hypotonic solutions causing dilution of body fluids. Moreover, balance studies indicate that except in severely injured patients salt retention is not marked. It is recommended, therefore, that salt be administered from the beginning in amounts of 5 to 10 grams daily. The more severely injured and the older patient with potential cardiac disease should receive the lower intake. Extra salt should not be administered on the basis of mild lowering of the plasma sodium unless it falls below 125 milliequivalents per liter.

Potassium metabolism offers no problem after head injury. There is no significant tendency toward retention or loss, and from catabolism of body protein there are usually about 30 milliequivalents available daily. It is unnecessary, therefore, to administer extra potassium in the posttraumatic period.

There is in most instances no urgency about insertion of a nasogastric tube for feeding purposes. Unless a significant degree of depletion was present before injury the patient can easily tolerate some nitrogen loss without ill effect. Moreover, as noted in the balance studies, utilization of administered nitrogen is very inefficient in the injured patient. Finally, with administration of tube feeding the solute load presented to the kid-

ney is significantly elevated and may lead to hypertonicity of body fluids producing the hypernatremic syndrome noted previously. Excessive protein feeding is probably the worst offender and therefore protein should not be given in amounts greater than 1.0 gram per kilogram of body weight. Simultaneously, the total fluid intake should be increased to about 3,000 cubic centimeters daily. In general, there is probably greater danger in starting tube feedings too early than in delaying for several days.

In the management of a patient who is comatose for a prolonged time, periodic checks on plasma concentrations of urea nitrogen, sodium, and carbon dioxide are advisable. This should be done at 3 day intervals during the first week and at least once during the second week. Mild lowering of plasma sodium is expected but marked lowering suggests water intoxication or salt depletion due to "salt wasting." In the latter the blood urea nitrogen is likely to be elevated. Elevation of plasma sodium suggests dehydration ("solute-loading hypertonicity" of Moore, 5) and extra water, while solutes are withheld, is necessary for its correction.

SUMMARY

Eleven patients have been studied by metabolic balance determinations of nitrogen, sodium, chloride, potassium, and water following head injuries of varying degrees of severity. On the basis of these observations certain recommendations are made for nutritional support of the patient with craniocerebral injury.

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APPENDICITIS IN OLDER PEOPLE

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As LONGEVITY in our society increases, it becomes necessary from time to time for us to re-examine the action of disease processes in older persons. The disease process to be discussed herein is appendicitis, its behavior in the elderly, a comparison of the disease in the elderly and control groups, and the application of these findings to improve diagnosis and treatment.

The matter of defining the age of the "older groups," or the "elderly," presents a problem. When does one become old? At what age do most people become physiologically old and different, so that a study of their disease would be significant and worth while?

Previous writers on the subject of appendicitis have considered that problems of the elderly began at age 39, 45, or 60 years. Since the aging process is a gradual one, we have arbitrarily selected the age of 50 years as the requirement for this group.

MATERIAL AND METHODS

The hospital records studied were of those patients aged 50 years and older who had undergone an appendectomy and in whom a diagnosis of appendicitis had been made. Between September 1, 1953 and September 3, 1958 there were 100 such cases of appendicitis at Mound Park Hospital.

There can actually be no control patients, in the true sense, yet to provide some comparison and to be consistent with previous studies on this subject, those patients in the fourth decade have been employed as a control group. During the period of this study, 95 patients in the fourth decade of life underwent an appendectomy. The first 50 patients in this age group provide an adequate sampling, are similar to other published groups, and serve for detailed comparisons in the tables included. Mound Park Hospital serves the city of St. Petersburg with its large group of elderly individuals from all corners of America. The surgery was performed by experienced attending surgeons from various training centers.

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This work was supported by the Mound Park Hospital Foundation, Inc.

OBSERVATIONS

There were 60,696 admissions to the hospital during the time of this study, making the rate of occurrence of appendicitis in the elderly 1.64 per 1,000 admissions.

There were 58 male patients (58 per cent) in the older group and 22 males (44 per cent) in the control series. Age distribution by decades was as follows: sixth, 35; seventh, 40; eighth, 19; ninth, 6.

Reviewing the hospital records did not always reveal detailed descriptions of symptoms, yet conclusions may be drawn as to the major complaints (Table I). Pain was the most common chief complaint in both groups. Seven per cent of those in the older group did not complain of pain, whereas all of those in the control group did. Vomiting and chills or fever were more frequent complaints in the older patients. Colp, as well as Wolff and Hindman, have mentioned the frequency and serious implication of chills with fever in the older patients. A quantitative analysis of the severity of symptoms or signs was not practicable in our study. Others have had the same experience. In reviewing the charts and tabulated symptoms, we were not so convinced as some investigators that the symptoms of appendicitis in the majority of elderly patients were greatly different from those in younger pa-

TABLE I.—SYMPTOMS

Symptoms	*Older group, per cent*	*Control group, per cent*
Pain	93	100
Nausea	69	74
Vomiting	46	36
Diarrhea	9	6
Constipation	9	8
Chills or fever	21	8
Anorexia	20	18
Other*	9	6

*Chiefly distention.

TABLE II.—DURATION OF SYMPTOMS PRIOR TO APPENDECTOMY AND ITS RELATION TO SEVERITY OF DISEASE

	50 plus year group		*Control group*	
Duration of symptoms, hrs.	*No.*	*No. with abscess or peritonitis*	*No.*	*No. with abscess or peritonitis*
0–24	46	11	35	5
24–48	23	14	8	3
48–72	7	5	1	0
72+	18	10	6	2
Insuff. data	6	2	0	0
Total	100	42	50	10

tients. This belief is corroborated by the fact that appendicitis was correctly diagnosed before operation in 84 of the 100 cases.

The duration of symptoms prior to appendectomy is shown in Table II which reveals that in the all-important first 24 hours of the disease, only 46 per cent of the older patients underwent an appendectomy as compared with 70 per cent of their juniors. In this regard the statistics of Wolff and Hindman indicate that perforation is not necessarily due to the delay, but rather to vascular and other factors in the older individual which limit the tissue reaction and defense mechanism from the start. Table II shows that there was spread of infection in a high number of patients in the senior group and that the incidence of spread increased after symptoms of 24 hours.

In the 50+ year group there were 37 patients with active concurrent disease. In the control group there were 9. Diabetes mellitus, cardiovascular disease, and peptic ulcer were the most common.

The preoperative diagnosis, recorded at the beginning of each operation, was "acute appendicitis" in 84 per cent of the senior group and in 90 per cent of the control. The preoperative leucocyte count was below 10,000 per cubic millimeter in 30 per cent of the 50+ year group and in only 14 per cent of the 30 to 39 year group. In all patients the appendix was removed. Drainage of the area was performed at the time of appendectomy in 37 of the 100 older patients, and in only 7 of the 50 control patients. This fact suggests that more advanced disease existed in those requiring drainage. A right lower quadrant, muscle-splitting incision (McBurney type) was used in 74 per cent of the control patients and in 58 per cent of the 50+ year group.

The stage of disease found at time of operation is recorded in Table III. The incidence of grossly visible perforations as described by the surgeon was quite high in the older group. In 4 cases perforation had occurred and no peritonitis or abscess was noted. It is interesting and important to know that there may exist: (a) perforation without peritonitis, such as occurs when omentum covers the perforation; or (b) peritonitis without gross perforation which may follow the passage of bacteria through an inflamed, but intact, appendix. The increased incidence of peritonitis and of perforation is highly significant by statistical calculation.

Antibiotics. In 39 per cent of the older group and 32 per cent of the controls antibiotic therapy was instituted 6 hours or more preoperatively. This 6 hour period was chosen arbitrarily, and it eliminates some patients who received antibiotics only immediately prior to surgery and thus would have no time to build up an effective blood level nor to show benefit therefrom. Postoperatively, antibiotics were received by 86 per cent of the older group and by 64 per cent of the control group. A combination of streptomycin (1 to 2 grams daily) and procaine penicillin (200,000 to 400,000 units daily) was the antibiotic preparation most used. Broad spectrum antibiotics were also employed. Among the 39 older patients receiving preoperative antibiotics, 22 (56 per cent) had either abscess or local or diffuse peritonitis. The fact that operation was

delayed those 6 hours or more during antibiotic therapy would indicate some lack of certain diagnosis at first. Antibiotics offered no demonstrable protection during the periods of preoperative observation.

Mortality and complications. Seven of the older group (and none of the controls) expired postoperatively. Three were in the seventh decade, 2 in the eighth, and 1 each in the sixth and ninth decades of life. The cause of death was: cardiac disease in 3 cases, bronchopneumonia in 2, hemorrhage from duodenal ulcer in 1, and aspiration pneumonia in 1. Major and minor postoperative complications are listed in Table IV. Mortality rates in other recent reports include: 9.9 per cent in Reeves' series of 66 patients aged 45 years and over; 2.3 per cent in that of Darling and McIver, consisting of 44 patients aged 50 years and over, 4.6 per cent in that of Goldenberg consisting of 126 patients aged 60 years and over, 4.2 per cent in the series of Hawk, Becker, and Lehman, consisting of 96 patients 50 years and over.

Pathologic diagnosis. The incidence of gangrene was greater in the elderly patients, 49 per cent as compared with 18 per cent in the control group. Statistically there is less than 1 chance in 100 that this difference is due to a sampling error. Acute appendicitis was the diagnosis in 44 per cent of the older group and in 68 per cent of the control group; subacute or chronic appendicitis, in 7 per cent of the older group and 4 per cent of the control group. These pathologic diagnoses were all confirmed by histologic examination. In a number of the hospital charts coded as appendicitis, a review of the histologic pattern was not conclusive for the diagnosis. Those cases of necessity were excluded from the series, although in some of them the disease may actually have existed and not have shown on the portions of appendix examined pathologically. In the few cases of chronic appendicitis that were included inflammatory cells within the various layers and mucosal or serosal changes were actually exhibited. This group did not include those which show only lymphoid hyperplasia and some fibrous thickening of the submucosa which some pathologists term chronic appendicitis.

TABLE III.—FINDINGS AT OPERATION

Gross findings	*Older group, per cent*	*Control, per cent*
Abscess or local peritonitis	30	10
Diffuse peritonitis	12	10
Gross perforation	46	18
Appendicitis only	54	80

TABLE IV.—POSTOPERATIVE COMPLICATIONS

Complication	*Older group No. of patients*	*Control No. of patients*
Wound infection	14	2
Peritonitis or peritoneal abscess	8	0
Dihiscence	0	0
Atelectasis or pneumonia	5	0
Others	19	5
Total No. of complications	46	7
No. of patients with complications	36	6

A review of all autopsies performed during the period of this study revealed that no patients died with undiagnosed appendicitis.

Economic factor. Since the economic aspects of medicine are yearly becoming of greater concern, the following data are presented, taken from an independent study made at this hospital. In 1956, appendectomy was performed upon 36 patients aged 50 years and over. The average period of hospitalization was 11.8 days. (One octogenarian stayed 33 days.) The average daily hospital bill was 26 dollars and 59 cents; the average total hospital bill was 313 dollars and 68 cents. Insurance paid for 43.2 per cent of the costs of hospitalization. The 26 patients in the sixth and seventh decades had insurance which paid 50.3 per cent of their hospital bills, whereas the 10 patients over 70 had only 27.6 per cent of the amount of their bills paid by insurance. These data and other facets of this study by the Mound Park Hospital Foundation show that those in the upper decades have the least coverage by insurance at a time of life when they are apt to need it the most.

SUMMARY AND CONCLUSIONS

1. An analysis of 100 cases of proved appendicitis in patients aged 50 years and older has been presented.

2. When compared to a control group of patients aged 30 to 39 years, the chief differences were found to be in: (a) symptoms of chills and fever, (b) the rise in leucocyte count, (c) interval of time prior to appendectomy, (d) severity of the disease, (e) the number requiring surgical drainage, (f) mortality, and (g) complications.

3. Failure of antibiotics to control the disease during observation is cited.

4. The older patients showed a very high incidence of perforation and of gangrene.

5. Appendicitis in older people is usually not dissimilar to that in younger individuals, yet there are significant differences which the physician must know.

6. Certain economic factors and the dearth of insurance coverage are shown.

7. The factor of age alone should be no deterrent to making the diagnosis of appendicitis nor to proceeding immediately with appendectomy.

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THE RECTUS ABDOMINIS MUSCLE AND THE EPIGASTRIC ARTERIES

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THE ANTERIOR ABDOMINAL WALL is encountered by the surgeon as frequently as any other region in the body. Therefore, the importance of familiarity with the anatomic detail of the parietal structures of the region is obvious. The aim of this study is to report upon a more comprehensive examination of the structure of the rectus abdominis muscles and their arteries of supply and to provide more structural information than is in standard textbooks of anatomy.

METHODS AND MATERIALS

Observations were based on dissections of 115 male and female cadavers in the anatomic laboratories at the Northwestern University Medical School.

Following each dissection, a plate of glass was placed over the muscle and arteries, and the structures were traced thereon. These sketches were then transferred to onionskin paper so that a full scale drawing of each specimen was available at the time of compilation of data.

Figures 6 and 8 were made by the artist directly from dissected specimens. The remaining figures are diagrammatic sketches emphasizing various anatomic differences.

RECTUS ABDOMINIS MUSCLE

The rectus abdominis is the ventromedial component of the abdominal musculature. It is a flattened, elongated muscle extending from its origin at the ventral surfaces of the fifth to seventh costal cartilages, the costoxiphoid ligament, and the lateral aspect of the xiphoid process to its insertion on the upper border of the superior ramus of the pubis, between the tubercle and the symphysis. The pubic attachment of the muscle is accomplished by a short tendon that is usually divided into a broad lateral portion and a more slender medial portion.

The longitudinal fibers of this muscle become aponeurotic in nature for short distances on the ventral surface of the muscle belly, thus forming the tendinous inscriptions. These take the form of irregular lines crossing the muscle transversely. Although they cannot be seen from the dorsal aspect of the muscle, their level may be detected by the slight indentation which they form at the muscle edge (Fig. 8). The inscriptions vary in width from their superior to their inferior edges, on different specimens and on the same specimen. In any angular inscription, the oblique portion is narrower than the horizontal portion in direct proportion to the magnitude of the angle that it forms with the horizontal. This is explained by the fact that the tendinous portion of each muscle fiber is the same length.

From time to time there has been controversy among anatomists[1] as to whether the

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[1]The rectus muscle first makes its appearance in the human 11 millimeter embryo. It is formed by buds from the dorsal myotomes, which fuse after growing into the membrana reunions. The myotomes involved, according to Bardeen (2), are the sixth, seventh, eighth, ninth, tenth, eleventh, and twelfth thoracic and sometimes the first lumbar.

Harrison (8) believed that the segments of a muscle like the rectus do not indicate that it arose from a corresponding number of embryonic muscle plates. Mall (8) stated, on the contrary, that the original segmental nature was retained in great part by the intercostal and abdominal muscles. Bardeen (1) thought it exceedingly probable that in the pig the tendinous inscriptions of the adult corresponded to the intermyotomic areas of the embryo and thus were of truly segmental origin. He evidently did not change this view in the case of human development (3).

The viewpoint that the tendinous inscriptions arise independently of the original myotomes, and that there is a period during which no segmentation is demonstrable, has recently been restated by Clark and Cullin and Brodel as opposed to the view of Grant that the inscriptions are indications of the segmental origin of the muscle. Even now a conflict of ideas exists as to the embryologic significance of the tendinous inscriptions.

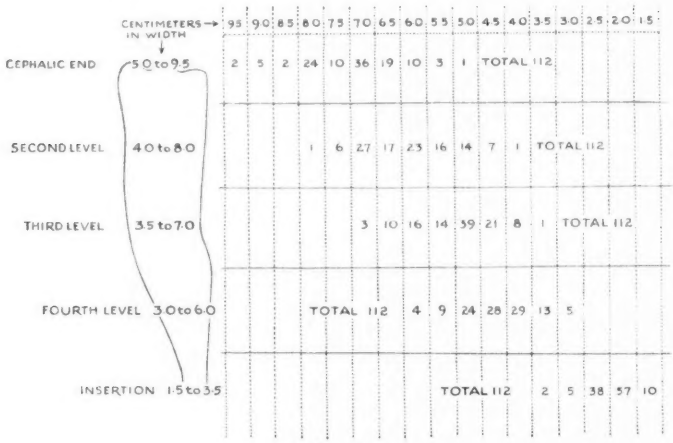

FIG. 1.

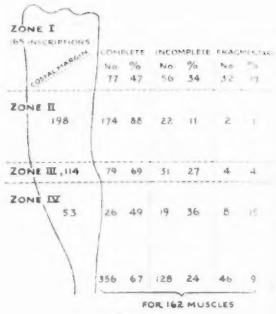

FIG. 2.

FIG. 1. The rectus abdominis muscle was quartered, and in 112 muscles the widths were measured at the upper and lower ends and the 3 intermediate levels. These widths at the various levels are listed in tabular form to the right of the drawing. The extremes in widths for the various levels are shown on the muscle.

FIG. 2. The arbitrary division of the rectus abdominis into 4 zones in which tendinous inscriptions are found, determined by the intersection of the costal margin with the lateral rectus border and the umbilical indentation. Information on whether the inscriptions of a given level are complete, almost complete, or fragmentary is tabulated to the right.

tendinous inscriptions are of truly segmental origin, representing the embryonic intermyotomic areas, or whether they are later acquisitions of the fetus, with no particular explanation for their presence.

Dimensions of the rectus abdominis. In most specimens examined, the two recti of a given body arose at the same level on the thoracic wall and were, therefore, of the same length; however, in 12 of 32 specimens (37.5 per cent) in which this measurement was observed, the difference in the length was more than 1 centimeter, and in some instances it was as great as 3 centimeters.

The length of the rectus muscles *in situ* was obtained by measuring the length of a string stretched from origin to insertion. Eighty-two of 112 lengths (73 per cent) were between 34 and 38 centimeters, whereas the extremes were 28 and 43 centimeters.

The length of the muscles was quartered, and the widths at the 5 levels thus determined were measured—the width of the thoracic origin, that of the tendon at its insertion, and the 3 intermediate widths. These measurements are summarized in Figure 1.

The longest muscles were not always the broadest. The 43 centimeter muscle was only 6.5 centimeters across at its origin, whereas the 28 centimeter muscle was 9 centimeters at the same level. The muscles tended to follow body types, short, wide recti being found in those specimens with that type of physique.

Tendinous inscriptions. These observations were based on 162 rectus muscles in 81 specimens. It was noted that all muscles had at least 1 inscription, and none had more than 4 inscriptions. Two (1 per cent) of the muscles had 1 inscription, 9 (6 per cent) had 2 inscriptions, 94 (58 per cent) had 3 inscriptions, and 57 (35 per cent) had 4 inscriptions. In 67 of 81 bodies (82 per cent), the number of inscriptions was the same bilaterally. A summary of the degree of bilateral symmetry can be found in the material presented in Table I.

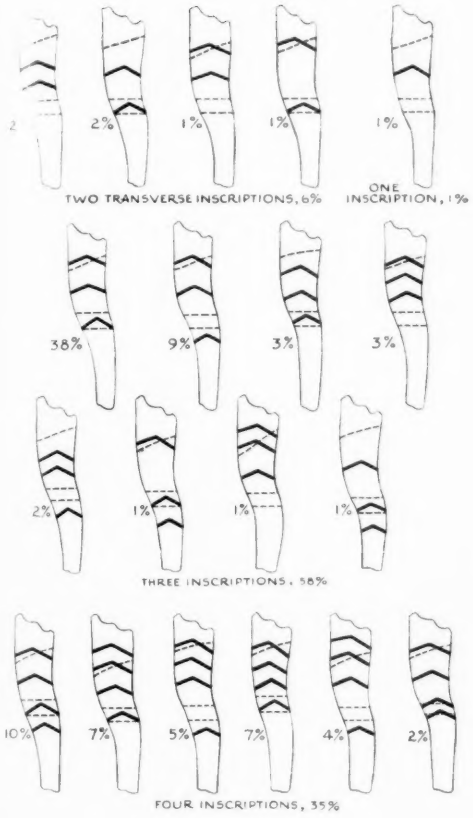

FIG. 3.

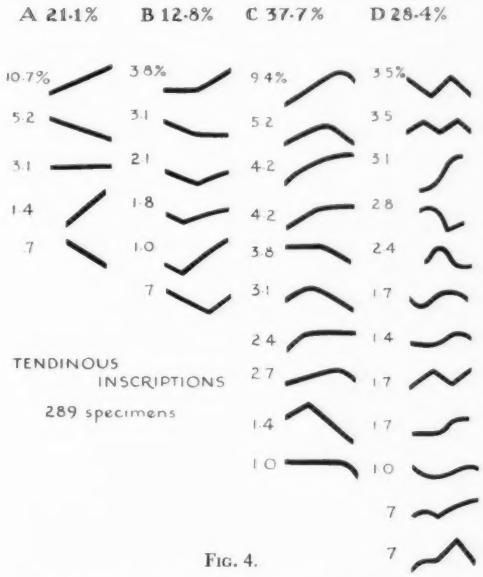

FIG. 4.

FIG. 3. A classification of the rectus muscles according to the number of inscriptions per muscle and the zones on the muscle in which they were found.

FIG. 4. A classification of 289 tendinous inscriptions into the 4 general types and the many subtypes. The reader is looking at the inscriptions as though they were seen on the right rectus. Type A is the straight line; B and C are simple curved or angled lines, with apices directed caudad or cephalad; and D, the more complex multiphasic type of inscription. The many subtypes make the statistical classification only relatively important. Examples seen only once are not included.

For the purpose of classifying the inscriptions according to their position on the rectus muscle, the muscle was divided into 4 zones (Fig. 2). The first zone consists of the upper portion of the muscle, from its origin to the intersection of the lateral border with the costal margin. The second zone extends from this point down to the umbilical indentation. The third zone is a 2 centimeter wide band at the umbilical level, and the fourth zone lies between the umbilicus and the tendon of insertion. Inscriptions that crossed these artificial dividing lines were placed either in the uppermost zone or in the umbilical zone, because each had to lie in part in one or the other, and none lay in both. Table II is an analysis of the number of inscriptions in each zone.

All inscriptions do not extend across the entire width of the muscle. Of the 530 inscriptions studied here, 356 (67 per cent) were complete, extending without interruption from the lateral to the medial muscle borders; 128 (24 per cent) were not complete but extended across more than half the width of the muscle, while 46 (9 per cent) were fragments less than half the width of the muscle. Of these 46 fragmentary inscriptions, the majority touched the lateral muscle border. For a co-ordination of the completeness of the tendinous inscriptions and their position on the muscle see Figure 2.

In addition to the number of inscriptions on each rectus, the muscles were further subclassified according to the distribution of these inscriptions in the previously defined

TABLE I.—DISTRIBUTION OF TENDINOUS INSCRIPTIONS TO RECTI IN A GIVEN SPECIMEN (81 BODIES)

No. of inscriptions	*No. of specimens*	*Per cent*
3 & 3	40	49
4 & 4	23	28
2 & 2	3	4
1 & 1	1	1
3 & 4	11	14
3 & 2	3	4

82 per cent bilaterally symmetrical.

TABLE II.—INSCRIPTIONS IN EACH OF THE FOUR ZONES OF THE RECTUS ABDOMINIS (FIG. 3) (162 MUSCLES)

	No inscription		*One inscription*		*Two inscriptions*	
Zone	*No.*	*Per cent*	*No.*	*Per cent*	*No.*	*Per cent*
I	17	11	125	77	20	12
II	2	1	122	75	38	24
III	50	31	110	68	2	1
IV	109	67	53	33	0	

TABLE III.—DISTANCE ALONG LATERAL BORDER OF RECTUS ABDOMINIS FROM COSTAL MARGIN TO FIRST TENDINOUS INSCRIPTION BELOW (162 MUSCLES)

No. of centimeters	*No. of muscles*	*Per cent*
2 (or less)	11	6.5
3	26	16.0
4	35	21.5
5	41	25.5
6	28	17.0
7	17	10.5
8	4	2.5

TABLE IV.—DISTRIBUTION OF DIFFERENT TYPES OF TENDINOUS INSCRIPTIONS ACCORDING TO ZONE OF RECTUS ABDOMINIS (162 MUSCLES)

	Type of inscription									
	A		*B*		*C*		*D*		*Fragment*	
Zone	*No.*	*Per cent*	*No.*	*Per cent*	*No.*	*Per cent*	*No.*	*Per cent*	*No.*	*Per cent*
I	36	22	18	11	45	27	34	21	32	19
II	26	13	12	6	104	53	54	27	2	1
III	31	27	21	18	28	25	30	26	4	4
IV	16	30	6	12	9	17	14	26	8	15

zones. The data collected on the number and distribution of inscriptions by zones are presented in Figure 3.

The distance along the lateral side of the rectus muscle, from the costal margin to the first inscription below, was determined and summarized in Table III.

The 484 complete or almost complete tendinous inscriptions were divided into four classes, according to their contour: (A) those that were straight lines, 109 (22.5 per cent); (B) those which were biphasic with their apices pointing caudad, 57 (12 per cent); (C) those which were biphasic with their apices pointing cephalad, 186 (38 per cent); and (D) the multiphasic type, 132 (27.5 per cent).

Two hundred eighty-nine of these inscriptions were then further subclassified into individual types, according to configuration. The frequency with which each type occurred is tabulated in Figure 4.

Finally, the different types of inscriptions were categorized according to the zone of the muscle in which they lay, and this information is presented in Table IV.

TABLE V.—DISTANCE FROM CREST OF PUBIS TO INTERSECTION OF INFERIOR EPIGASTRIC ARTERY WITH LATERAL BORDER OF RECTUS ABDOMINIS (OR MEDIAL BORDER OF HESSELBACH'S TRIANGLE) IN 162 MUSCLES

Distance, cm.	*No. of specimens*	*Per cent*
0*	1	0.5
2	3	2.0
3	7	4.5
4	17	10.5
5	19	11.5
6	28	17.0
7	49	30.0
8	24	15.0
9	10	6.0
10	4	2.5

*In 1 instance the epigastric artery remained entirely behind the tendon of the rectus, and thus there was no triangle of Hesselbach.

TABLE VI.—DISTANCE BETWEEN POINTS AT WHICH SUPERIOR AND INFERIOR DEEP EPIGASTRIC ARTERIES ENTERED MUSCLE SUBSTANCE OF 162 RECTI ABDOMINI

	Body halves	
Distance, cm.	*No.*	*Per cent*
Visible anastomosis	1	0.5
1 to 5	37	23.0
5 to 10	70	43.0
10 to 15	37	23.0
15 to 22	14	8.5
Superior epigastric absent	3	2.0

EPIGASTRIC ARTERIES[2]

Inferior epigastric artery. The deep inferior epigastric artery arises from the external

[2]In the 6 week old human embryo the superior and inferior epigastric arteries, along with the internal mammary arteries, form paired longitudinal vessels that extend the length of the ventral wall of the fetal trunk. As shown by Mall (9), the vessels are a connecting link at the terminations of the lower segmental arteries, and their homologues in the cervical region are the vertebral arteries.

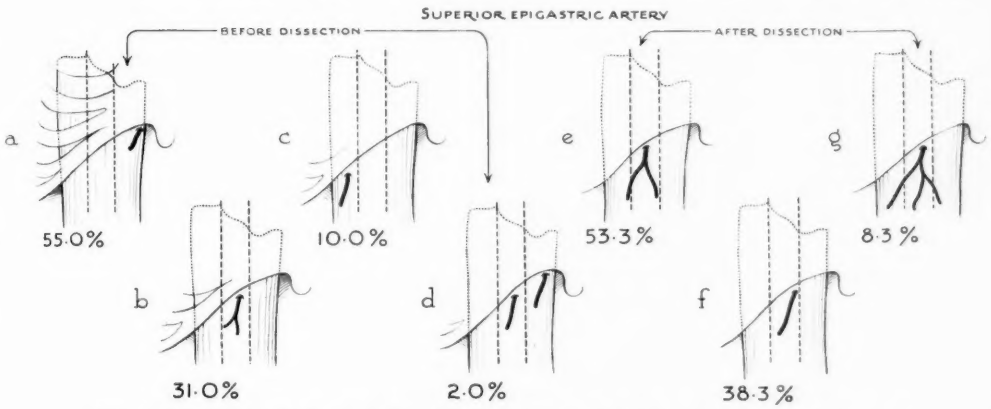

FIG. 5. The position of the superior epigastric artery on the dorsal aspect of the left rectus before dissection is shown in a, b, c, and d. Although the vessel frequently appears as 2 stems, they are seen only occasionally in different thirds (d). The configuration of the vessel after dissection is shown in e, f, and g.

iliac artery just before it passes beneath Poupart's ligament, and approaches the rectus abdominis from its lateral aspect. The distance from the insertion of the rectus tendon to the intersection of this artery with the lateral rectus margin—the medial side of Hesselbach's triangle—was measured and the variations recorded in Table V. In 1 case the artery lay dorsal to the tendon and muscle entirely, and thus there was no triangle.

As the vessel passed superiorly on the dorsal aspect of the rectus, it was found to consist of a single main stem in 139 (86 per cent) instances, and of a double main stem in 23 (14 per cent) instances before entering the muscle substance in the lower third 28 times (17 per cent), in the middle third 126 times (78 per cent), and in the upper third 8 times (5 per cent).

Superior epigastric artery. The superior epigastric artery is the direct downward continuation of the internal mammary artery. It was seen on the dorsal surface in 97 of 100 rectus abdominis muscles when they were severed and reflected cephalad. In 3 specimens the vessels were absent or buried in muscle tissue. In 53 of the 162 specimens, the vessel appeared on the muscle as 2 stems. With the muscle divided into thirds longitudinally, the region of the muscle on which the superior epigastric was first found as it emerged from the costoxiphoid space was recorded and is illustrated in Figure 5.

A visible anastomosis of the superior and inferior deep epigastric arteries was found without benefit of dissection in only 1 instance. In the remainder of cases the distance between the vessels as they entered muscle substance was recorded in Table VI.

There was a significant branch to the umbilicus in 20 of 100 muscles.

Lateral terminations of the epigastric arteries. Nerves, arteries, and veins pass between the posterior aspect of the rectus abdominis and the posterior wall of the rectus sheath, as shown in Figure 6. These structures may run singly or in any combination, but they are usually found in tetrads consisting of a small artery, a nerve, and 2 veins enclosed in a ribbon of fat and connective tissue. Laterally, the nerves and vessels pass through the fibrous semilunar lines into the plane between the transversus abdominis and internal oblique muscles.

There were 541 arteries leaving the posterior aspect of 160 rectus muscles, the number ranging from none to 6 per muscle (Table VII). In 100 body halves these arteries were classified in terms of that portion of sheath which they left (Fig. 1). Of these vessels, 3 per cent left the rectus

TABLE VII.—DISTRIBUTION OF RECTUS MUSCLES ACCORDING TO NUMBER OF ARTERIES LEAVING POSTERIOR ASPECT TO ENTER LATERAL ABDOMINAL MUSCULATURE IN 160 BODY HALVES

No. of arteries	*Body halves*	
	No.	*Per cent*
1	8	5
2	20	13
3	63	39
4	46	29
5	18	11
6	5	3

TABLE VIII.—DISTRIBUTION OF 541 ARTERIES LEAVING POSTERIOR ASPECT OF RECTUS ABDOMINIS MUSCLE IN 160 BODY HALVES, ACCORDING TO ASSOCIATED INTERCOSTAL NERVE

Nerve level	*No. of arteries*	*Per cent of total*
7	6	1.0
8	6	1.0
9	68	12.5
10	195	36.0
11	165	30.5
12	43	8.0
No associated nerve	58	11.0

TABLE IX.—FATE OF ARTERIES LEAVING RECTUS SHEATH FROM LATERAL SIDE

Nerve level	*No. of arteries at level*	*Arteries not found in lateral abdominal musc.*		*Arteries ended in lateral abdominal wall*		*Arteries anastomosed in lateral abdominal wall**	
		No.	*Per cent*	*No.*	*Per cent*	*No.*	*Per cent*
No nerve	58	38	65.5	20	34.5		0
7	6		0		0	6	100
8	6	1	17	2	33	3	50
9	68	28	41	28	41	12	18
10	195	54	28	101	52	40	20
11	165	56	34	90	54.5	19	11.5
12	43	21	49	20	46.5	2	4.5
Total and per cent	541	198	37.0	261	48.0	82	15.0

*Eight of the vessels, 6 at the eleventh level and 2 at the twelfth level, anastomosed not with the corresponding intercostal but with the deep circumflex iliac artery.

TABLE X.—MANNER OF TERMINATION OF ARTERIES ENDING IN LATERAL ABDOMINAL WALL

Nerve level	*No. of arteries at level*	*Transversus abdominis*	*Internal oblique*	*Both muscles*	*Along intercostal nerve*
No nerve	20	5	14	1	0
8	2	2	0	0	0
9	28	22	3	0	3
10	101	57	35	2	7
11	90	24	56	7	3
12	20	2	17	0	1
Total No.	261	112	125	10	14
Per cent		43	48	4	5

sheath opposite the upper quarter of the muscle, 60 per cent from the next quarter below, 28 per cent from the third quarter, 1 per cent from the lowermost quarter, and 9 per cent at about the center of the muscle.

Although the intercostal nerves have formed a plexus in the lateral abdominal wall (4), it is possible to classify the arteries as accompanying the fibers of a specific spinal nerve in most instances (Table VIII).

Dissections of the abdominal wall were made and the vessels further studied in the lateral abdominal musculature in 160 body halves. Of the 541 arteries leaving the posterior aspect of the rectus abdominis, 198 (37 per cent) did not go beyond the linea semilunaris; 261 (48 per cent) passed through the linea semilunaris and entered the lateral abdominal musculature, but did not anastomose with intercostal arteries; and 82 (15 per cent) anastomosed with their respective intercostal arteries or the deep circumflex iliac artery. For a co-ordination of the termination of the arteries with nerve levels, see Table IX.

Of 261 arteries that ended in the lateral abdominal musculature, the majority had a course of less than 2 centimeters after leaving the linea semilunaris, whereas the remainder could be followed for 3 to 6 centimeters before they terminated. The great majority of the vessels radiated from the sheath in a course parallel to that of the nerves at an angle of 45 to 60 degrees. These vessels ended in 1 of 4 ways: 112 (43 per cent) entered the transversus abdominis; 125 (48 per cent) entered the internal oblique; 14 (5 per cent) terminated after following a course near the nerve without entering either muscle; and 10 (4 per cent) sent equal twigs to both muscles. For a tabulation of the

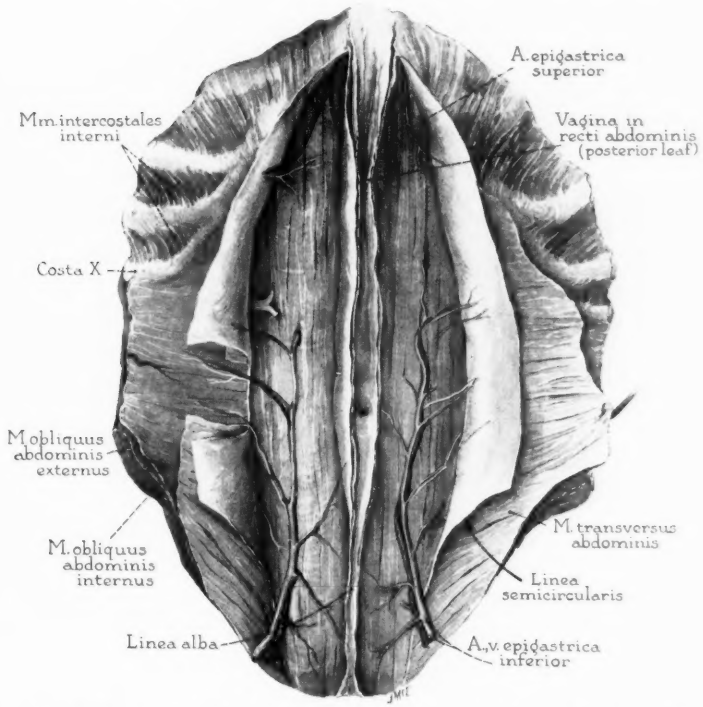

FIG. 6. The internal (posterior) aspect of the rectus muscle, epigastric vessels, and intercostal nerves. A portion of the sheath with transverse abdominal muscle has been removed to reveal the course of muscular rami of the inferior epigastric vessels between the intermediate and deep layers of the anterolateral abdominal musculature. The superior epigastric artery descends between the xiphoid process of the sternum and the seventh costal cartilage. Entering the substance of the muscle, its course is largely intramuscular. It anastomoses with the inferior epigastric artery, according to Spaelteholz, "in the neighborhood of the navel," but present studies showed the anastomosis regularly at a more cranial level. The inferior epigastric artery arises from the external iliac immediately above the inguinal ligament and follows a curving course, at first obliquely medialward, then vertically upward. Along its course, the artery at first lies medial to the abdominal inguinal ring, then crosses the tendinous (inferomedial) portion of the transversus abdominis muscle and reaches the dorsal surface of the rectus muscle. The artery lies just external to the peritoneum until it enters the rectus sheath at the level of the linea semicircularis. For a variable distance it merely follows the posterior surface of the rectus muscle, then tunnels into the latter's substance and establishes the anastomosis with the superior epigastric within the muscle.

manner of termination of the vessels that ended in the lateral abdominal musculature, see Table X. This table demonstrates the relatively greater magnitude of the transversus abdominis in the upper abdomen and of the internal oblique in the lower abdomen.

The arteries that were anastomotic with intercostal or circumflex iliac arteries were usually of fine, uniform caliber, running the distance across the lateral abdominal wall near their corresponding intercostal nerves.

Arterial patterns within the rectus abdominis. In 30 pairs of recti, the muscle substance was dissected away from the epigastric arteries. The patterns of branching and their frequency of occurrence for the superior epigastric are shown in Figure 5e, f, g, and

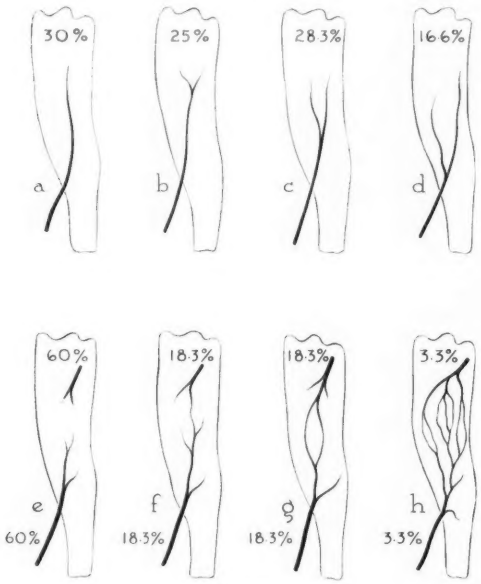

FIG. 7.

FIG. 7. The frequency of various configurations of the inferior epigastric artery after dissection are shown in a, b, c, and d. The lower set of figures shows the anastomoses or absence thereof as revealed by dissection: e, no anastomosis; f, 1 anastomosis; g, 2 anastomoses; and h, multiple anastomoses.

FIG. 8. The rectus muscles with the epigastric arteries dissected. A special dissection of a specimen with many anastomoses between superior and inferior epigastric arteries. This dissection also illustrates the manner in which arteries tend to follow the tendinous inscriptions.

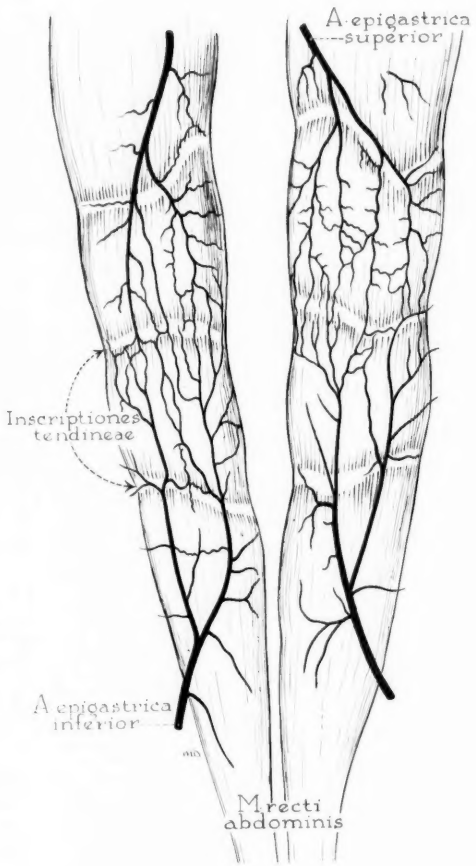

FIG. 8.

for the inferior epigastric in Figure 7a, b, c, d. After dissection, substantial branches to the umbilicus and small branches to the tendon were found in most specimens.

In the 60 completely dissected body-halves there were 215 arteries passing into the lateral body wall. Of these, 206 (96 per cent) arose from the inferior epigastric, and 9 (4 per cent) left the superior epigastric. Of those leaving the superior epigastric, 4 were at the seventh nerve level, 2 at the eighth nerve level, and 3 at the level of the ninth thoracic nerve. The total number of inscriptions in the 60 muscles was 178, and of these, 56 (31 per cent) had vessels of significant caliber imbedded in their substance for some part of their length. This phenomenon is demonstrated in Figure 8, a drawing of a specimen with a particularly large number of epigastric branches and anastomoses.

After dissecting muscle bundles away from the vascular patterns, gross anastomoses of the superior and inferior epigastric arteries were found in 24 (40 per cent) of the muscles. The absence or presence, and the variation in number, of anastomoses is tabulated in Figure 7e, f, g, and h.

SUMMARY

The data collected in this study make it possible to arrive at certain general conclusions.

The rectus muscles are variable in length and width, tending to parallel body build in their relative dimensions. In the majority of cases the two recti are of equal length, and measure between 34 and 38 centimeters.

The two rectus muscles in a given individual usually have the same number of inscriptions, and in half of the bodies in this series the number was 3 on each side. No muscle had more than 4 inscriptions.

Although the majority of inscriptions extend completely across the muscle, some are slightly shorter or only fragmentary in length.

For purposes of study, the muscle was divided into 4 arbitrary zones. The first zone occupied the area of the costal margin and above; the second extended from costal margin to umbilicus; the third was a narrow band at the umbilicus, and the fourth extended from the umbilicus to the tendon of insertion.

The most frequent location for an inscription was the second zone, and there were often 2 inscriptions at this location. On the other hand, there was no inscription in the lowest zone in over half the muscles examined.

The commonest number of inscriptions on a muscle was 3, and these were located chiefly in zones I, II, and III (38 per cent of muscles examined in this series).

Tendinous inscriptions most frequently took the geometric form of simple angles or curves, and the angle or curve most often had its apex directed cephalad. The distribution of the various types of inscriptions to the muscle zones was unremarkable, except that the fragmentary inscriptions were more common at the upper or lower ends of the muscles.

The deep inferior epigastric artery was present in all bodies bilaterally, most frequently as a single-stem vessel lying on the posterior aspect of the rectus, and entering the substance of the muscle in its middle third.

The superior epigastric artery is occasionally not seen on the dorsal surface of the rectus, being either absent or buried in muscle tissue. When present, it is usually a single stem that enters the medial portion of the muscle after a short course on the surface.

In only 1 instance, in this series of 162 muscles examined, did the superior and inferior epigastric vessels anastomose on the surface of the rectus muscle in the pattern frequently depicted in anatomy texts. Furthermore, when muscle fibers had been dissected away from the arteries, only 40 per cent of the superior and inferior epigastric arteries were found to have any gross anastomoses.

Three or 4 small branches of the inferior epigastric artery commonly pass laterally through the linea semilunaris into the plane between the transversus abdominis and internal oblique muscles of the abdomen. These vessels usually leave the middle two-fourths of the muscle from its posterior aspect, and they most frequently accompany branches of the ninth, tenth, or eleventh thoracic nerves. These vessels were dissected out to their termination, and it was found that only 15 per cent anastomosed with intercostal or circumflex iliac arteries. The remaining vessels terminated most commonly in the transversus abdominis in the upper abdomen and in the internal oblique in the lower abdomen.

Finally, the data on arterial anastomoses were re-examined to discover whether there was an increased number of anastomoses between epigastric and intercostal vessels in those bodies with grossly demonstrable anastomoses between superior and inferior epigastric arteries. It was found that there was no increased tendency for such anastomoses to occur between epigastric and intercostal vessels when grossly demonstrable connections between the superior and the inferior epigastric arteries were present.

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THE REPLACEMENT OF SHORT SEGMENTS OF VEINS WITH FUNCTIONAL AUTOGENOUS VENOUS GRAFTS

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DISEASED AND DAMAGED VEINS have been infrequently replaced with grafts, whereas a similar direct attack on arteries has become an accepted surgical procedure. Clinical situations in which venous replacements have been advocated or used include: obstruction of the superior vena cava, cancerous invasion of major veins, extensive carcinomas of the pancreas requiring partial excision of the portal and superior mesenteric veins during radical pancreatectomy, portal hypertension in which grafts may be necessary to approximate the portal and inferior vena caval system, and injuries to major veins.

The materials evaluated as venous replacements have been arterial homografts, plastic tubes, venous homografts, and venous autografts. In general, the patency rate has been acceptable only when venous autografts have been used.

To date, grafting procedures in the venous system have been directed only toward restoring a conduit through which blood could pass. The status of the valves has not been recorded in experimental studies. However, a normal functioning vein not only holds blood, but also has valves which insure a unidirectional flow. In most situations this valvular function is not necessary. However, in replacing veins of the lower extremities an ideal functional graft should contain competent valves.

In searching for functional grafts, the material has been selected which theoretically offered the greatest chance for success—the autogenous vein. Short segments of canine femoral veins have been replaced with a portion of the contralateral vein. Phlebography and careful gross and histologic studies have not only been used to determine patency but also to determine the functional status of the grafts.

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METHODS

Adult mongrel dogs were anesthetized with sodium pentobarbital, intubated with an intratracheal tube, and placed on their backs to expose both femoral triangles.

In 7 dogs a technique of performing venous anastomoses was developed by dividing and resuturing their femoral veins about 3 centimeters below the inguinal ligament under sterile precautions. Important points in the technique include the following: (1) the division of the vein obliquely; (2) the careful removal of any adventitia near the site of anastomosis; (3) the occlusion of the veins by a rubber shod bulldog clamp; (4) the avoidance of grasping the vein with any instrument; (5) the use of very fine arterial silk, preferably No. 6-0 black braided silk with a 3/8 inch tapered swedged-on needle; (6) the use of 2 everting mattress stay sutures with a continuous over-and-over everting stitch between the stays; (7) the irrigation of the vessel with a heparinized saline solution before completing the anastomoses.

In 20 dogs, a 3 to 5 centimeter segment of either the right or left femoral vein was excised and sutured into a 1 to 2 centimeter defect in the opposite femoral vein as an end-to-end graft. The same careful technique for performing the anastomoses was used. Care was taken to avoid tension on the grafts themselves. The grafts contained 1 or 2 valves. When the anastomoses were completed the patency of the graft and

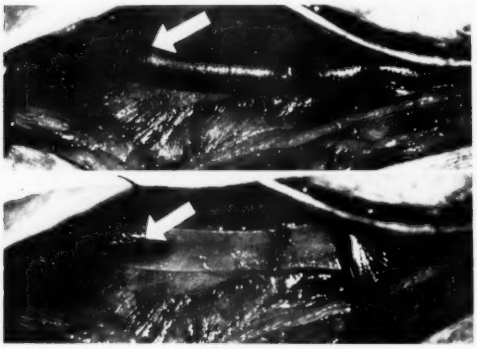

FIG. 1.

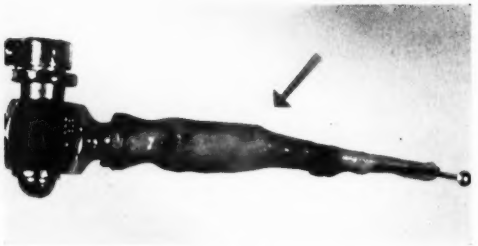

FIG. 2.

FIG. 1. Above, Postoperative appearance of an autogenous venous graft is shown. The arrow points to a valve. Below, Competency of the valve has been demonstrated by stripping the blood from the graft with the tips of two clamps and then releasing the superior clamp. Retrograde blood flow occurs until it reaches competent valve pointed out by arrow.

FIG. 2. Competency of a valve in an autogenous venous graft at the time of autopsy is demonstrated. The blunt adapter of a stopcock has been inserted into the superior end of the vein and the injected saline distends the vein at the site of a competent valve pointed out by the arrow.

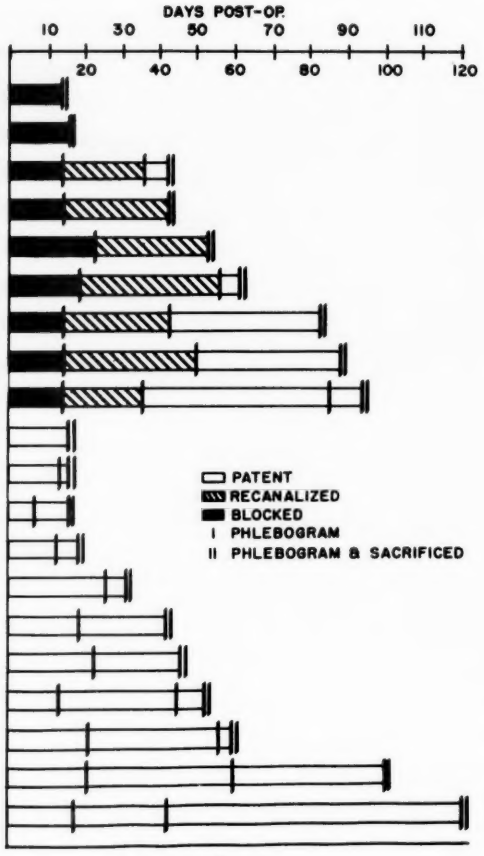

FIG. 3.

FIG. 3. Patencies of end-to-end autogenous venous grafts.

competency of the valves were evaluated by stripping the blood from the graft and then releasing the vein superiorly, allowing blood to flow backward into the graft until it reached a competent valve (Fig. 1). In approximately one-half of the dogs regional heparinization with 50 milligrams of heparin in 500 cubic centimeters of saline was carried out for 2 to 3 hours postoperatively.

Phlebograms utilizing 50 per cent miokon were performed 2 to 3 weeks after the operation and at 4 to 6 week intervals thereafter. At the time of sacrifice, the grafts and adjacent femoral veins were carefully removed. A cannula was inserted into the proximal end of the vein and saline slowly injected into the end to test the competency of the valves (Fig. 2). The veins were then opened and gross observations made of the vein walls and valves. Longitudinal histologic sections using a Verhoeff stain counterstained with van Gieson were made to include the suture line and adjacent valves.

RESULTS

Division and resuturing. The femoral vein was divided and resutured in 14 extremities of 7 dogs. These procedures were devised to develop a satisfactory technique for the

anastomosis of veins. The results reflected the learning process. Seven of the 14, or 50 per cent of the anastomoses performed, were obstructed 2 to 3 weeks after operation, and all 7 failures occurred in the first 10 procedures. Phlebograms were performed on 3 of the 7 occluded anastomoses 4 to 6 weeks later at which time the grafts were patent. Therefore, 10 of the 14 anastomoses, or 71 per cent, were patent 6 to 8 weeks after operation. They remained patent for periods up to 7 months postoperatively.

End-to-end autogenous venous grafts (Fig. 3). Short segments of autogenous femoral venous grafts were used to replace defects in the opposite femoral veins of 20 dogs. Eleven of the 20, or 55 per cent of the grafts, were patent 14 to 21 days after operation.

Two animals were sacrificed when their first phlebograms, performed 14 and 16 days after operation, indicated obstruction of the graft. The grafts were filled with a friable thrombus adherent to the suture lines (Fig. 4). Histologic studies demonstrated a marked acute and chronic inflammatory response in the wall of the vein, particularly adjacent to the suture line, and organizing thrombi adherent to the intimal surfaces. Valves could not be demonstrated by gross or histologic examinations.

Seven of the grafts were occluded at the time of the first phlebogram but were found to be patent by phlebograms or autopsies 42 to 94 days postoperatively (Fig. 5). The grafts were thickened and narrowed, and with 1 exception competent valves could not be demonstrated by the retrograde injection technique. The intimal surfaces were smooth and glistening without gross evidence of residual thrombi but either no valves or shortened and thickened valves were seen. Histologic sections revealed thickening of the media and adventitia, and increased vascularity and round cell infiltration which were most apparent near the suture lines. These changes were less apparent in the older grafts. Small plaques of re-endothelized organized thrombi, commonly laden with hemosiderin pigments, were present in almost all of the specimens (Fig. 6). The valves visualized were shortened and thickened and demonstrated increased vascularity and round cell infiltration (Fig. 7). The single normal appearing valve was the grossly competent valve previously mentioned.

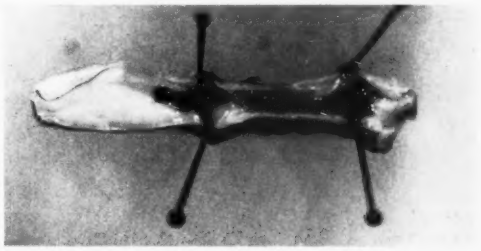

FIG. 4.

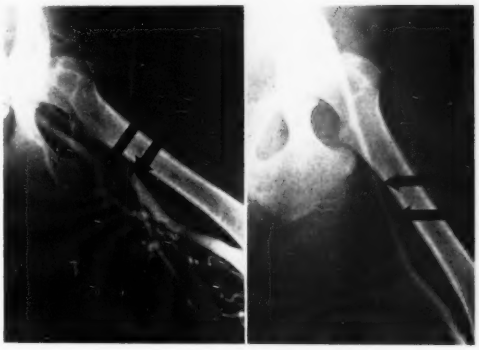

FIG. 5.

FIG. 4. An autogenous venous graft which was thrombosed at autopsy 14 days postoperatively is pictured. Note the extensiveness of the thrombosis at the suture line.

FIG. 5. Phlebogram on the left was performed 14 days after short segment of the femoral vein was replaced with an autogenous venous graft and demonstrates obstruction of graft (between arrows) with extensive collateralization. Phlebogram on the right was of the same extremity 35 days postoperatively and demonstrates a patent graft.

Eleven of the grafts were patent at the time of the first phlebogram and remained open for periods up to 4 months (Fig. 8). At autopsy the grafts appeared thin walled. Competent valves were demonstrated in 9 of the 10 grafts known to contain valves at the time of the original operation. The intimal surfaces were smooth and glistening,

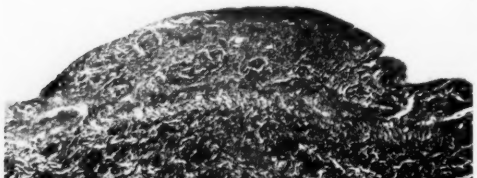

FIG. 6.

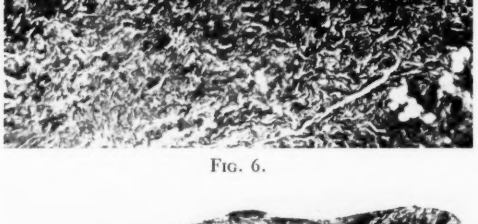

FIG. 7.

FIG. 8.

FIG. 9.

FIG. 6. Section of the wall of a recanalized vein demonstrating a re-endothelized organized thrombus (plaque), ×38.

FIG. 7. Section of a recanalized 61 day old vein graft which demonstrates a thickened and shortened valve, ×44. There is increased vascularity, connective tissue, and round cell infiltration in the entire vein wall including the valve. The valve was incompetent grossly.

FIG. 8. Phlebogram of patent graft (between arrows) 97 days postoperatively. Phlebogram at 14 days was similarly patent.

FIG. 9. A 121 day old graft which was patent throughout the postoperative period.

and thin nonadherent valve leaflets could be demonstrated (Fig. 9). Histologic examinations revealed minimal inflammatory response in the vein wall, even at the site of the sutures. The valves visualized were normal (Fig. 10).

Ten dogs had short term regional heparinization after the operation and in 6 the grafts thrombosed. In 4 of 10 dogs not heparinized thrombosis of the grafts developed.

DISCUSSION

Previous experimental studies reported by Bryant and associates, Daniel, and Sauvage and Wesolowski have indicated that autogenous veins can be very successfully used as grafts in the venous system. The degree of success has been based, in general, on patency rates of grafts several weeks postoperatively. Phlebographic and histologic evidence has not been presented to indicate whether the grafts have been patent

throughout the postoperative period or whether they recanalized. In our experiments 55 per cent of the grafts were patent by phlebography 2 to 3 weeks postoperatively. All of the grafts which were studied by phlebography 5 or more weeks postoperatively were patent even if they had been obstructed at 2 to 3 weeks. Unfortunately, the grafts which had been obstructed by a thrombus demonstrated the adverse effects of recanalization. There was thickening and increased vascularity of the media and adventitia and small portions of organized clots had become incorporated into the wall of the vein as plaques or "cushions" as described by Robertson, Perrett, Colbeck, Moore, and Blair. Of more importance these recanalized veins had incompetent valves grossly, and on histologic examination the valves had either become shortened and thickened or incorporated into organized clots, as described by Edwards and Edwards. The appearance of the recanalized veins was markedly different from the normal appearance of the veins which had never been obstructed. The unobstructed vein grafts were the only grafts which could be classified as functional grafts and therefore, the "functional graft patency rate" was 55 per cent.

The 18 grafts which were observed for longer than 3 weeks were all patent 8 weeks after the operation. If our first phlebograms had been obtained at this later time, as has evidently been the custom of Schauble and associates, the "graft patency rate" would have been 100 per cent in our series. It would seem important to us that in future experiments in this field the graft patency rate be determined within 3 weeks after the operation, or else histologic studies at the time of sacrifice should be recorded to rule out the possibility of recanalization. An obstructed graft which ultimately becomes patent has few adverse effects in the femoral vein of the experimental animal. However, in clinical situations such as the replacement of resected portal, superior mesenteric, or common femoral vein, or the bridging of the portal and caval venous system, even a temporarily obstructed graft may cause irreversible damage. In addition, should vein grafts be used to replace postphlebitic veins in the lower extremity their main value would be the introduction of valves into the deep venous system and in that case the functional graft patency rate and not simply the graft patency rate would assume increased importance.

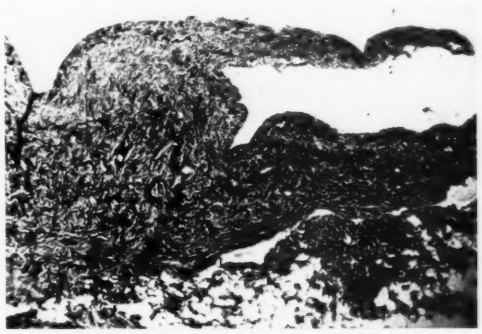

FIG. 10. Section of 47 day old graft which had been patent throughout the postoperative period, ×39. Note the normal valve and thin vein wall.

Short term regional heparinization did not affect the patency rate in these experiments. It has been our impression as well as others' that the success of grafting procedures in the venous system is more dependent upon a standard delicate technique.

CONCLUSIONS

1. Autogenous veins were used to replace short segments of the femoral veins of 20 dogs.

2. A 55 per cent functional graft patency rate was obtained as determined by patent phlebograms throughout the postoperative course and gross and histologic evidence of competent valves at autopsy.

3. A standard delicate technique of anastomosis was thought to be essential. The use of short term regional heparinization did not lower the thrombosis rate.

4. Grafts which were thrombosed 2 to 3 weeks after operation and observed for longer periods did recanalize and become

patent but they contained incompetent valves.

5. The evaluation of any venous replacement graft should include early postoperative phlebograms and/or histologic studies at the time of autopsy.

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DIAGNOSIS AND RESULTS OF TREATMENT IN GASTRIC POLYPS

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THE MAJORITY of gastric tumors that come to the attention of the surgeon are malignant, and their true nature is suspected by the internist, diagnosed by the roentgenologist, recognized by the surgeon, and confirmed by the surgical pathologist. Diagnostic errors seldom occur when the tumor is large, but this is less true when the tumor is small. Thus, it is usually impossible for the clinician or roentgenologist to be certain whether a gastric polyp is entirely benign or actually harbors malignant changes. Just as the clinician and the roentgenologist experience difficulty in establishing the true diagnosis preoperatively, so the surgeon at operation may be uncertain regarding the existence of malignant changes in a gastric polyp until histologic examination is done.

PRESENT STUDY

The present study was undertaken with the hope of learning something regarding the diagnosis and treatment of gastric polyps. With this purpose in mind, a review was made of the records of 465 patients in whom the clinical diagnosis of gastric polyp was made at the Mayo Clinic from 1925 through 1951. Follow-up studies ranging from 5 to 32 years after operation were made on those patients treated surgically. The term "gastric polyp," as commonly used, probably has more of an anatomic than a pathologic connotation. Its use in the present report refers primarily to adenomatous polyps, although some patients who had inflammatory polyps, undoubtedly, were included in this review.

The 465 patients in this study were divided into the following three groups: (1) those in whom the clinical diagnosis of gastric polyp was made but on whom operation was not performed (165 patients); (2) those on whom operation was performed and in whom a diagnosis of adenomatous gastric polyp or polyps was confirmed by the surgeon (206 patients); (3) those on whom operation was performed and in whom the clinical diagnosis of adenomatous gastric polyp proved to be in error (94 patients).

Since the diagnosis was established on clinical and roentgenologic evidence alone in the patients in group 1, it is apparent that this group no doubt includes some patients who actually had other types of lesions. In contrast, a definite histologic diagnosis of polyps was established in all patients in group 2. This group is divided into two subgroups, namely: 181 patients proved to have benign adenomatous lesions on histologic examination and 25 patients found to have adenomatous polyps with zones of adenocarcinoma graded 1 or 2 (Broders) at the tip without invasion of the stalk (Fig. 1). This gives an incidence of cancer of approximately 12 per cent in those 206 patients who at the time of operation appeared to have benign adenomatous polyps. The patients in group 3 had a variety of lesions other than adenomatous polyps, including polypoid carcinoma, malignant lesions of different types, and various other benign gastric lesions. Carcinoma is found grossly at times in association with gastric polyps (Fig. 2).

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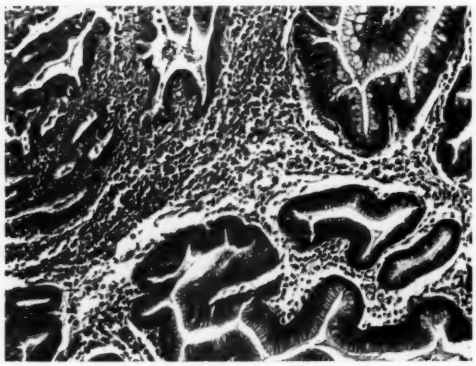


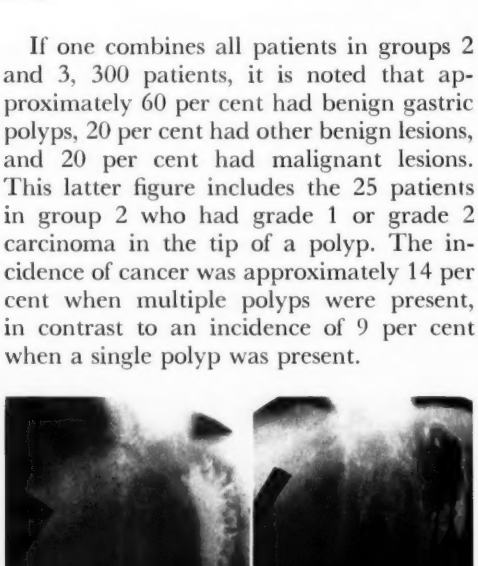
FIG. 1.

FIG. 1. Low grade malignant changes in a gastric polyp. Hematoxylin and eosin, ×68.

FIG. 2. Surgical specimen of resected stomach, showing gross carcinoma in association with multiple gastric polyps.

FIG 2.

If one combines all patients in groups 2 and 3, 300 patients, it is noted that approximately 60 per cent had benign gastric polyps, 20 per cent had other benign lesions, and 20 per cent had malignant lesions. This latter figure includes the 25 patients in group 2 who had grade 1 or grade 2 carcinoma in the tip of a polyp. The incidence of cancer was approximately 14 per cent when multiple polyps were present, in contrast to an incidence of 9 per cent when a single polyp was present.



a b

FIG. 3. Roentgenograms following ingestion of barium. a, Polyps in prepyloric portion of stomach; operation not performed. b, Roentgenogram made 3 years later showing carcinoma in prepyloric portion of stomach.

CLINICAL ASPECTS

The clinical findings in group 2, those patients in whom diagnosis was confirmed at operation, were reviewed. The patients ranged in age from the second to the ninth decade of life, the majority being between the fifth and seventh decades; the average age was approximately 56 years. There was no pronounced sex incidence; 107 were males and 99 were females. Symptoms for the most part were vague and nonspecific, being described as postcibal fullness, epigastric gnawing or burning, belching, gas, and flatulence. Bleeding from the gastrointestinal tract, either hematemesis or melena, was infrequent, occurring in only 5 per cent of the patients. A history resembling that of ulcer was noted in 5 per cent of the patients. Pernicious anemia was an associated finding in 20 patients, about 10 per cent. Obviously, the clinical history and symptoms are not of much help in establishing the diagnosis of gastric polyp.

The physical findings were for the most part not significant. A palpable abdominal mass was found in 13 patients, although it was considered certain that it was not the polyp or polyps that constituted this mass. Varying degrees of loss of weight were reported by approximately 15 per cent of

the patients. The value for hemoglobin in 48 per cent of these 206 patients was less than 13 grams per 100 milliliters of whole blood; 13 per cent of the group had moderately severe anemia, with hemoglobin levels of less than 10 grams. The incidence of achlorhydria, as determined by a modified Ewald meal, is great in patients who have gastric polyps, being from 3 to 3½ times higher than that in comparable members of the "normal" population. In the present group, this incidence was 80 per cent.

Gastroscopic studies were done on 38 patients. A diagnosis of benign polyp was made 28 times; other diagnoses included gastric ulcer, malignant polyp, gastritis, and an indeterminate or negative examination. It is apparent that gastroscopy is not used frequently in our experience in patients thought to have gastric polyps.

ROENTGENOLOGIC ASPECTS

Roentgenologic examination after the ingestion of barium was the most reliable and frequently employed diagnostic procedure. For the purpose of evaluating the accuracy of roentgenologic diagnosis, the surgical and pathologic findings were considered in 227 patients in whom the roentgenologist made the preoperative diagnosis of "gastric polyp or polyps," with no qualifying remarks regarding possible cancer or other types of lesions. For the most part, these patients were in group 2. Some were in group 3, but in many instances in this latter group the roentgenologist included some qualifying phrase in addition to the diagnosis of gastric polyp or polyps.

Many difficulties are encountered in the roentgenologic recognition and differential diagnosis of small gastric polyps, and it could hardly be expected that this diagnosis could be made with the same degree of accuracy as that of gastric ulcer or carcinoma. When a single gastric polyp was diagnosed by the roentgenologist, a single lesion of some type was found by the surgeon in 138 (82 per cent) of 169 patients (Table I). When the roentgenologic diagnosis was multiple polyps, multiple lesions of some type were found in 79 per cent of such patients. It is possible that in some of these patients the surgeon may have identified only a single lesion when 1 or more other small lesions were present, but unrecognized.

TABLE I.—ACCURACY OF ROENTGENOLOGIC DIAGNOSIS OF SINGLE OR MULTIPLE GASTRIC POLYPS RELATED TO SURGICAL FINDINGS

Roentgenologic diagnosis	*Cases**	*Surgical findings*		*Roentgenologic diagnosis same as surgical findings, per cent*
		Single lesion	*Multiple lesions*	
Single polyp...	169	138	31	81.7
Multiple polyps	58	12	46	79.3

*Comprises 227 patients treated surgically.

TABLE II.—ACCURACY OF ROENTGENOLOGIC DIAGNOSIS RELATED TO TYPE OF GASTRIC POLYP FOUND AT OPERATION

Roentgenologic diagnosis	*Cases**	*Surgical findings*		*Accuracy of roentgenologic diagnosis, per cent*
		Gastric polyp or polyps	*Other lesions*	
Single polyp.....	169	106	63	62.7
Multiple polyps..	58	51	7	87.9

*Comprises 227 patients treated surgically.

TABLE III.—ROENTGENOLOGIC DIAGNOSIS OF GASTRIC POLYPS AND INCIDENCE OF MALIGNANCY

Roentgenologic diagnosis of gastric polyp	*Cases**	*Pathologic diagnosis*		*Incidence of cancer, per cent*
		Benign lesion	*Malignant lesion*	
Single.....	169	135	34	20.1
Multiple.....	58	48	10	17.2

*Comprises 227 patients treated surgically.

Of the 169 patients in whom the roentgenologic diagnosis of a single polyp was made, 106 patients (63 per cent) actually had 1 or more gastric polyps. Of the 58 patients in whom the roentgenologic diagnosis of multiple polyps was made, 51 patients (88 per cent) actually had gastric polyps (Table II). Apparently the roentgenologic diagnosis of multiple polyps is more accurate than is that of a single polyp.

It is of interest to the internist and surgeon to have some idea of the chance of finding a lesion that is actually malignant when the roentgenologist makes a diagnosis of single or multiple gastric polyps. A malignant lesion was found in 34 of the 169 pa-

TABLE IV.—5 YEAR SURVIVAL RATES IN PATIENTS WITH CLINICAL DIAGNOSIS OF GASTRIC POLYPS

*Classification of patient**	*Treatment*	*Patients*		*Lived 5 years or more after diagnosis*	
		Total	*Traced*	*No.*	*Per cent†*
Group 1.....	Medical management	165	110	75	68.2
Group 2a....	Surgical removal	176	150	138	92.0
Group 2b....	Surgical removal	24	23	18	78.3
Group 3.....	Surgical removal	89	74	53	71.6

*Group 1—gastric polyp diagnosed clinically and patient treated medically; group 2a—benign polyp removed and diagnosis verified by pathologist (5 hospital deaths); group 2b—adenocarcinoma in tip of polyp surgically removed and verified by pathologist (1 hospital death); group 3—benign and malignant lesions surgically removed that proved to be other than benign adenomatous polyps (5 hospital deaths).

†Based on traced patients. Inquiry as of January 1, 1957. In the 3 surgical groups, hospital deaths are excluded in the calculation of survival rates.

TABLE V.—5 YEAR SURVIVAL RATES OF PATIENTS WITH BENIGN GASTRIC POLYPS

Surgical findings	*Patients*		*Lived 5 years or more after operation*	
	Total	*Traced*	*No.*	*Per cent**
Single polyp.....	91	77	72	93.5
Multiple polyps....	85	73	66	90.4
Total.....	176	150	138	92.0

*Based on traced patients. Inquiry as of January 1, 1957. Hospital deaths are excluded in the calculation of survival rates.

tients (20 per cent) in whom the roentgenologist diagnosed a single gastric polyp (Table III). When the diagnosis was that of multiple gastric polyps, a malignant lesion was found in 17 per cent of the patients.

SURGICAL ASPECTS

It has been relatively common practice in past years when a single gastric polyp was diagnosed preoperatively and a single polyp was found at operation for the surgeon to do a transgastric local excision of the polyp. A similar type of operation has been used fairly often when 2 or perhaps more polyps were present. If the pathologist reported some evidence of malignant change in the tip of the polyp without invasion of the pedicle, frequently nothing further was done surgically. On the other hand, if a definite malignant lesion was present that invaded the base of the polyp or the wall of the stomach, partial gastrectomy was carried out as for any other small malignant gastric lesion. In some patients in whom multiple polyps were present, partial gastrectomy has been performed. In some instances, extensive partial gastrectomy has been done in order to remove all polyp-bearing gastric mucosa. In other cases, less extensive resection has been performed, and polyps remaining in the cardia of the stomach have been fulgurated or excised locally through the open end of the stomach. It has not been considered advisable to perform total gastrectomy for benign gastric polyps. Of the 206 patients in group 2, a total of 99 underwent local excision, 94 had partial gastrectomy, and the remainder underwent some other type of surgical procedure. The operative mortality rate for the 206 patients of group 2 on whom operation was performed for benign or malignant gastric polyps was 2.9 per cent.

LATE RESULTS

Follow-up studies were made on all patients (Table IV). A total of 110 patients in group 1 (no operation) was followed; 75 patients (68 per cent) were living 5 years or more after the clinical diagnosis of gastric polyp or polyps was made. An accurate pathologic diagnosis was not established in these patients, since operation was not performed. It is interesting to note that 92 per cent of the 150 traced patients, group 2a, who had benign gastric polyps removed survived 5 years or more after operation. As noted previously, only 25 patients, group 2b, had polyps removed that evidenced carcinoma in the tip. One hospital death occurred in this group. Twenty-three patients were traced, of whom 78 per cent survived 5 years or more after operation. In group 3, 5 hospital deaths occurred among the 94 patients who had a variety of benign and malignant lesions removed. Of the remaining 89 patients, 74 were traced, and 72 per cent of these survived 5 years or more after operation.

Late results in the patients who had surgical treatment for gastric polyps also may be considered in relationship to whether

the polyps were single or multiple. Such a study reveals that the 5 year survival rate in these two groups is virtually identical, being 93 per cent in the former group and 90 per cent in the latter (Table V).

Since the 5 year survival rate for patients who had benign gastric polyps removed by either local excision or partial gastrectomy is virtually identical with the survival rates for normal people of the same age and sex, a comparison of the survival rates of those with local excision and those undergoing partial gastrectomy would not be significant.

COMMENT

It is apparent that the clinical diagnosis of gastric polyp or polyps, which in fact is based on the roentgenologic diagnosis in virtually all cases, is less accurate than is the diagnosis of most other gastric lesions. This is reflected by the fact that approximately 20 per cent of the 300 patients in whom the diagnosis of gastric polyp or polyps was made had malignant lesions at the time of operation. In some of these patients, 25 of 59, the malignant lesion was found in the tip of a gastric polyp; however, in the remainder, a more extensive malignant process was found. In our opinion, when a roentgenologic diagnosis of gastric polyp or polyps is made, the possibility of a malignant tumor being present is sufficiently great that operation should be advised if the patient is in a reasonably good general condition. While it is difficult to demonstrate definitely that gross gastric carcinoma may start in, and develop from, a gastric polyp, the existing evidence is extremely suggestive that this may occur (Fig. 3). The surgeon must realize that gross inspection alone may not be adequate to detect the presence of malignancy in what appears to be a benign gastric polyp. Microscopic study of the removed specimen is required. The surgeon also must be mindful of the fact that multiple gastric polyps may be present even though the roentgenologist has described only a single polyp. On the other hand, the roentgenologist is seldom in error when he describes multiple lesions. The frequency of development of malignancy in a benign polyp is estimated variously in different viscera. The incidence in gastric polyps in the present study was approximately 12 per cent. Evidence suggests that this process may be more extensive than only malignant change in the tip of the polyp (Fig. 3).

Decision by the surgeon regarding performance of local excision rather than partial gastrectomy when there is no gross or histologic evidence of malignancy probably rests largely upon the number of polyps present. When many polyps are encountered, partial gastrectomy may appear to be a more satisfactory type of procedure than are multiple local excisions. In either case, one should be certain to remove all polyps at operation. In most patients, if malignant change is found in the polyp, partial gastrectomy is usually advisable.

SUMMARY

The records of 465 patients in whom the clinical diagnosis of gastric polyp was made at the Mayo Clinic have been reviewed. Operations were performed on 300 of these patients. The surgical pathologic findings revealed that 60 per cent of the 300 patients had benign gastric polyps, 20 per cent had other types of benign lesions, and 20 per cent had malignant lesions. This last group included, among others, 25 patients in whom malignant changes were found in the tip of a gastric polyp. Roentgenologic examination is the most accurate diagnostic procedure, but it is less accurate in gastric polyps than in most gastric lesions.

A follow-up study of 5 years or more after operation was made on all patients. A total of 92 per cent of the patients who had benign gastric polyps removed were alive 5 or more years later. This is equivalent to the survival rate of the "normal" population of the same age and sex distribution. The survival rate was 78 per cent for those who had polyps removed which showed malignant changes in the tip.

A STUDY OF THE DISTRIBUTION OF ASCORBIC ACID IN THE WOUND HEALING OF GUINEA PIG TISSUE

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A ROLE FOR ASCORBIC ACID has long been implicated in the formation of connective tissue, this having recently been reviewed by Bourne. The means by which ascorbate functions in the healing wound is unknown. Nutritional levels of ascorbate have been correlated with the tensile strength of healing wounds by Lanman and Ingalls, Bartlett, Jones, and Ryan, and Wolfer, Farmer, Carroll, and Manshardt, collagen formation by Robertson and Schwartz, cicatrization by Hunt, and with various other parameters as noted by Edwards and Dunphy. One experimental approach to this problem has involved observing histologic and chemical changes during the healing of surgically induced wounds under different conditions of ascorbate availability.

We were interested in determining whether the available ascorbate in the body was redistributed during wound healing and whether the dietary ascorbate was preferentially localized in any tissue. The ascorbic acid concentrations of various tissues were determined in normal and scorbutic guinea pigs after an abdominal incision had been made.

MATERIALS AND METHODS

Male guinea pigs weighing 300 to 400 grams were divided into 4 groups. The normal controls were fed ad libitum a diet consisting of rabbit pellets and lettuce. The diet was supplemented daily with a multivitamin mixture containing about 25 milligrams of ascorbic acid. A muscle-splitting right rectus incision was made from costal margin to symphysis pubis, and the wound carefully sutured with interrupted No. 4-0 silk through the anterior sheath, rectus muscle, and peritoneum. The skin was separately closed. Animals were sacrificed at 1, 2, 3, 4, 5, 7, 9, 11, 14, or 21 days after the operation. Various tissues were excised and analyzed for ascorbic acid according to the method of Roe, Mills, Oesterling, and Damron. Wound tissue was obtained by excising the tissue within the sutures throughout the length of the incision.

A second group of animals was maintained on the vitamin C deficient diet described by Sherman supplemented with a similar multivitamin mixture containing all necessary vitamins except ascorbic acid. These animals were operated on 14 days after beginning the ascorbate deficient diet, utilizing the same technique, and groups of animals were sacrificed at the same intervals as the normal controls.

The third group was treated the same as the second group. Seven days after the operation, however, these animals received 1 dose of either 0.5, 2, 10, or 25 milligrams of ascorbic acid administered intramuscularly. These guinea pigs were sacrificed at intervals of 1, 2, 4, 8, 24, 48, or 72 hours after injection.

The fourth group consisted of guinea pigs which were put on the scorbutigenic diet but were not operated upon. They were autopsied at 1, 2, 3, 4, 5, 7, 9, 11, 14, or 21 days after being put on the deficient diet.

Ascorbic acid concentrations were determined in wound tissue, normal rectus

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Supported by Grant No. RG4656(C2) from the Division of Research Grants & Fellowships, National Institutes of Health, Public Health Service, Washington, D. C.

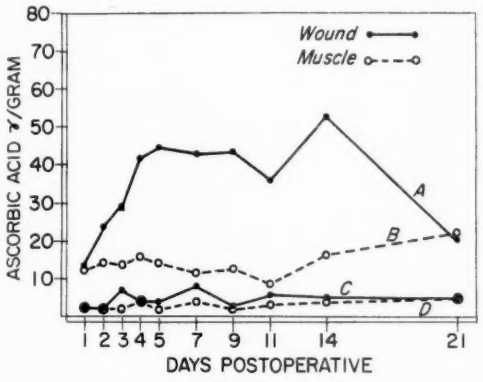


FIG. 1.

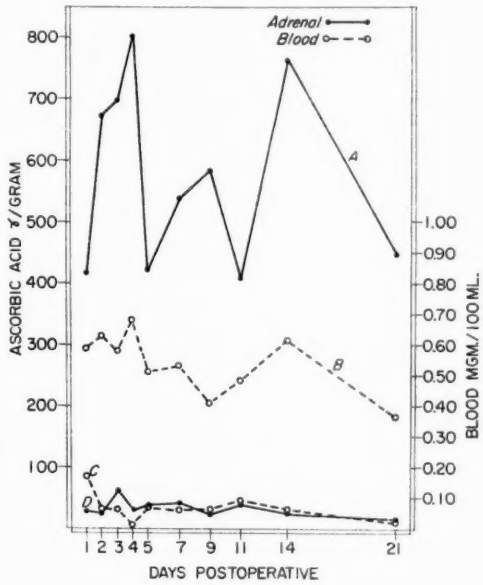


FIG. 2.

FIG. 1. The ascorbic acid concentration in wound and muscle tissue from animals operated upon. Curves *A* and *B* are results from guinea pigs on a normal diet. Curves *C* and *D* are results from guinea pigs on a scurvy diet. Each point represents the mean value of from 7 to 12 animals.

FIG. 2. The ascorbic acid concentration in adrenal and blood from animals operated upon. Curves *A* and *B* are results from guinea pigs on a normal diet. Curves *C* and *D* are results from guinea pigs on a scurvy diet. Each point represents the mean value of from 7 to 12 animals.

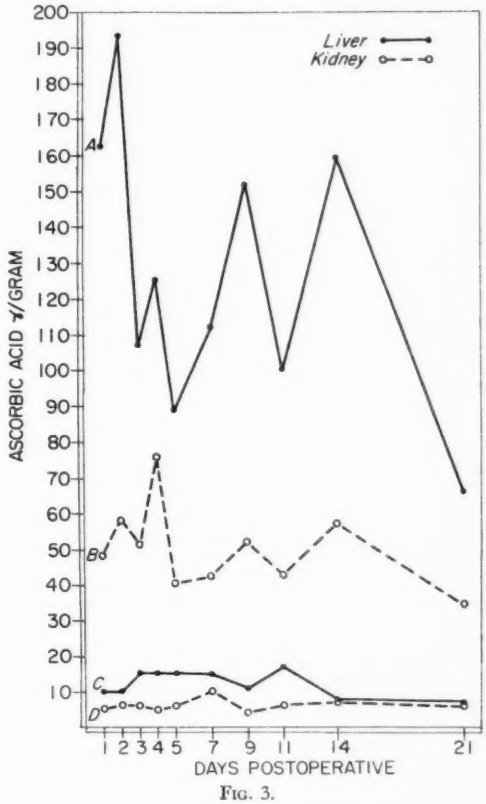


FIG. 3.

FIG. 3. The ascorbic acid concentration in liver and kidney from animals operated upon. Curves *A* and *B* are results from guinea pigs on a normal diet. Curves *C* and *D* are results from guinea pigs on a scurvy diet. Each point represents the mean value of from 7 to 12 animals.

muscle, kidney, liver, adrenals, and blood. The results are reported in gamma of ascorbic acid per gram of tissue (wet weight) for all tissues except blood which is reported as milligrams per 100 milliliters of blood.

RESULTS

In the intact muscle of normal guinea pigs the ascorbate concentration remained fairly constant (Fig. 1). The day to day variation was not statistically significant. In contrast, the wound tissue began to concentrate ascorbic acid on approximately the second postoperative day. Peak levels of ascorbate were maintained in wound tissue until beyond the fourteenth day. The ascorbate concentration returned to that of the uninjured tissue by the twenty-first postoperative

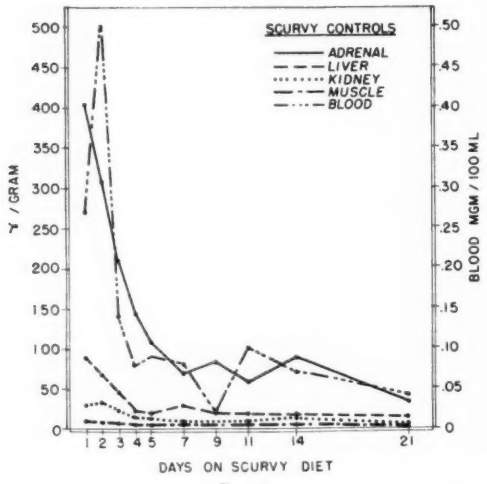


FIG. 4.

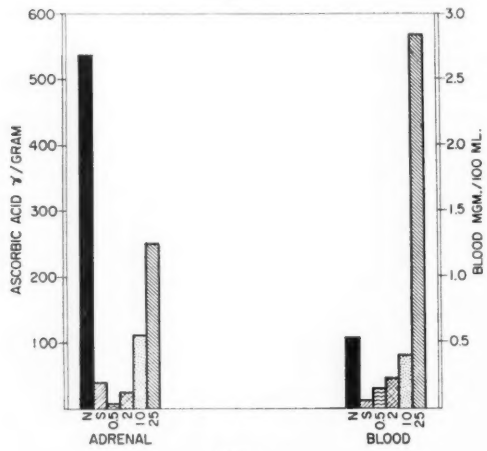
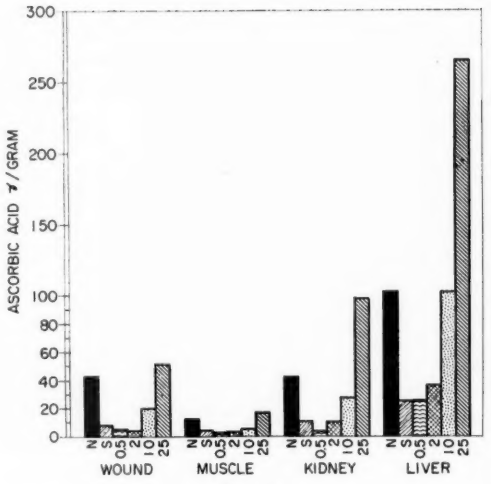


FIG. 5.

FIG. 4. The ascorbic acid concentrations of tissues from nonoperated upon guinea pigs maintained on a scurvy diet. Each point represents the mean value obtained from 4 to 6 animals.

FIG. 5. The ascorbic acid concentration in adrenal and blood from normal (*N*) and scorbutic (*S*) guinea pigs on the seventh postoperative day compared with the ascorbate concentration 1 hour after the intramuscular administration of 0.5, 2, 10, or 25 milligrams of ascorbic acid. Each value represents the mean obtained from 4 to 12 animals.



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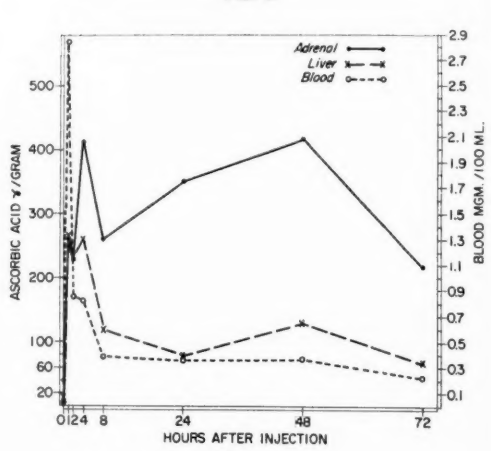

FIG. 7.

FIG. 6. Ascorbic acid concentration in wound, muscle, kidney, and liver from normal and scorbutic guinea pigs on seventh postoperative day compared with ascorbate concentration 1 hour after intramuscular administration of 0.5, 2, 10, or 25 milligrams of ascorbic acid. Each value is the mean from 4 to 12 animals.

FIG. 7. Ascorbic acid concentrations in adrenal, liver, and blood at various intervals after injecting 25 milligrams of ascorbate into scorbutic guinea pigs on the seventh postoperative day. Each point represents the mean value obtained from 7 to 12 animals.

day, a time which corresponded to a completely healed wound histologically. Blood levels remained fairly constant (Fig. 2) as did kidney tissue (Fig. 3). Although the mean values for liver (Fig. 3) fluctuated somewhat, the changes were found not to be statistically significant. As others have established, the adrenals from normal guinea pigs contained the highest ascorbate concentration of any tissue (Fig. 2).

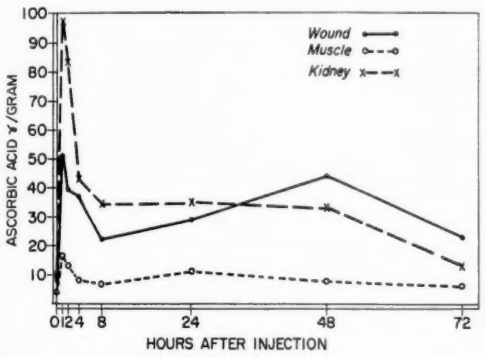

FIG. 8.

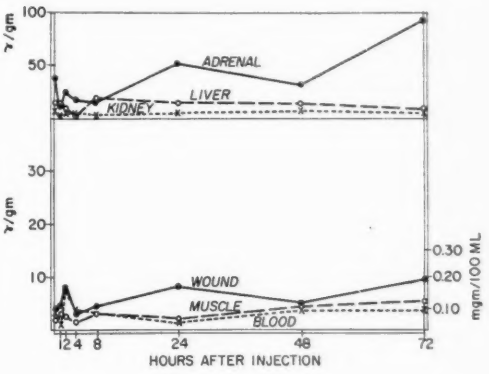

FIG. 9.

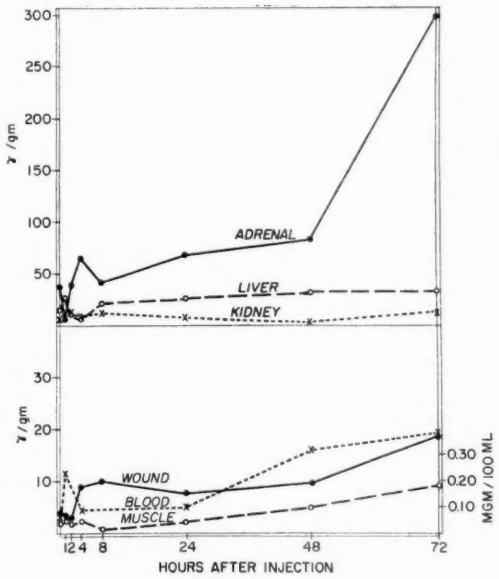

FIG. 10.

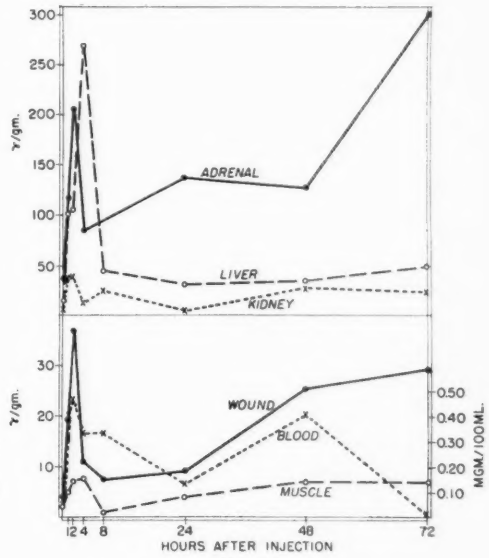

FIG. 11.

FIG. 8. Ascorbic acid concentrations in wound, muscle, and kidney at various intervals after injecting 25 milligrams of ascorbate into scorbutic guinea pigs on the seventh postoperative day. Each point represents the mean value obtained from 7 to 12 animals.

FIG. 9. Ascorbic acid concentrations in tissues at various intervals after injecting 0.5 milligram of ascorbate into scorbutic guinea pigs on the seventh postoperative day. Each point represents the mean value obtained from 4 animals.

FIG. 10. Ascorbic acid concentrations in tissues at various intervals after injecting 2 milligrams of ascorbate into scorbutic guinea pigs on the seventh postoperative day. Each point represents the mean value obtained from 4 animals.

FIG. 11. Ascorbic acid concentrations in tissues at various intervals after injecting 10 milligrams of ascorbate into scorbutic guinea pigs on the seventh postoperative day. Each point represents the mean values obtained from 4 animals.

All tissues from scorbutic animals contained only trace amounts of ascorbic acid (Figs. 1 to 3). The rate at which the tissues were depleted of vitamin C may be seen in Figure 4. Ascorbic acid administered intramuscularly was rapidly absorbed into the blood stream (Fig. 5) and taken up by the various organs. Within 1 hour after 25 milligrams of ascorbate were injected, wound, muscle, kidney, and liver contained

from 130 to 260 per cent of that found in corresponding tissues from normal animals on the seventh postoperative day (Fig. 6). At 1 hour after injection, the adrenal concentration increased 6 fold (Fig. 5), and after 4 hours approached that found in the normal (Fig. 7). Within a few hours after injection, the ascorbate levels of the tissue fell off rapidly but remained above the scorbutic levels. The wound took up more ascorbic acid per gram of tissue than the adjacent intact muscle.

At least 2 milligrams of ascorbate had to be injected before the tissue concentrations began to increase above that of the untreated scorbutic guinea pigs (Figs. 7 to 11).

DISCUSSION

The literature is replete with experimental studies relating ascorbic acid to the process of wound healing. Whether the healing is followed histologically, by tensile strength, or by other means, ascorbate has been found to be necessary for normal healing. Where and how this vitamin acts is unknown.

These experiments were carried out to determine the distribution of ascorbic acid during healing. Apparently, in animals kept on a steady regimen, the ascorbate concentration does not vary much in intact tissues except in the adrenals. The adrenal ascorbate level is known to vary under different conditions of adrenal function such as in stress. In these experiments, the fluctuating adrenal levels could not be correlated with the needs of the healing wound. The vitamin was, however, concentrated in the wound tissue in contrast to the intact muscle. In wounded scorbutic animals treated with a single injection of ascorbate, the latter was rapidly taken up by the tissues studied. Again the wound concentration surpassed that of the neighboring, uninjured tissue. While this does not define the function of ascorbate, nor prove that it acts directly in the wound, it again suggests that the vitamin does have an action directly in the injured tissue. Further experiments are being carried out in an attempt to localize and define the role of ascorbic acid.

SUMMARY

Determinations of the ascorbic acid level in the wound, muscle, liver, kidney, adrenals, and blood of normal and scorbutic guinea pigs were made at intervals up to 21 days after operation. The wound tissue showed a significant increase in ascorbate during the healing period. A single injection of ascorbic acid into the wounded scorbutic animal on the seventh postoperative day produced a rise in ascorbate in all tissues, particularly the wound.

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RESPONSES OF PLATELETS, EOSINOPHILS, AND TOTAL LEUCOCYTES DURING AND FOLLOWING SURGICAL PROCEDURES

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STUDIES concerned with the behavior of circulating platelets during and following surgical procedures show wide discrepancies in results. Hueck reported a slight but inconstant thrombocytopenia during the first few postoperative days, followed by thrombocytosis beginning on the seventh postoperative day. Dawbarn and associates found thrombocytosis beginning on the sixth postoperative day and reaching a maximum on the tenth postoperative day. Sulger and Bozzin and Willinsky also described an increase in platelet levels during the immediate postoperative period in some patients, but a decrease in others. In contrast, Allen found no changes in platelet levels postoperatively. These investigators (1927 to 1932) used indirect counting methods to determine platelet levels.

Evans and Fowler, using direct counting methods, reported no changes in numbers of platelets during the first 2 or 3 postoperative days, whereas Wright found thrombocytopenia on the first postoperative day and pronounced thrombocytosis from the fourth to tenth postoperative days. Potts and Pearl found a slight postoperative thrombocytosis, but Adams reported marked thrombocytosis beginning from the tenth to fifteenth day after surgery. More recently, Warren and associates observed a considerable decrease in platelet levels during and immediately following extensive surgical procedures. Although these latter observations were made on patients who received blood transfusions during the operations, it was concluded that the thrombocytopenia was due to the stress of surgery and not to the blood loss. Krevans and Jackson found no change in platelet levels following surgery in patients who did not receive blood transfusions, but reported a mild thrombocytopenia in patients who received less than 5,000 milliliters of blood during the operations. They attributed this thrombocytopenia to factors other than stress, such as dilution of the recipient's platelets and the presence of platelet isoagglutinins and thrombocytopenogenic substances.

In contrast to these findings, Mustard investigated nontransfused, surgical patients and reported approximately a 10 per cent increase in the platelet levels during and immediately after extensive surgical procedures.

The purpose of the present report is to describe hourly and daily variations of platelet, eosinophil, and total leucocyte levels during and after extensive and less extensive surgical procedures in patients with and without blood transfusions.

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Supported by the Sequoia Hospital Research Fund.

MATERIALS AND METHODS

Eighteen patients were included in the study. Eleven patients underwent elective extensive surgical procedures, and 7 had less extensive operations. Their ages were from 15 to 65 years. The various operations performed ranged from a dilation and curettage, lasting 15 minutes, to a combined thoracolaparotomy lasting 4 hours, and included radical mastectomy, gastric and colonic resections, total hysterectomy, and arthrotomy. All procedures were performed under anesthesia with sodium pentothal and

nitrous oxide. All patients had previously undergone thorough physical examinations, and were found to be in good general physical condition (except for their surgical condition) and were free from infections. Six of the 11 patients undergoing extensive operations received blood transfusions during the procedures with amounts of blood given ranging from 500 to 1,500 milliliters. A timetable was kept as to when the blood transfusions were given and the platelet counts obtained in order to establish any existing relationship. No attempt was made to correlate any alterations in platelet levels with the amount of blood loss, since it had been previously established that changes in platelet counts following hemorrhage were less significant as compared with those following surgical operations.

Platelet, eosinophil, total white blood cell counts, and differential white cell counts were done on the day before operation, immediately after induction of general anesthesia, every hour during the operations, 2 and 4 hours after surgery, and then daily thereafter. All daily postoperative counts were performed between 12:00 noon and 1:00 p.m. in order to avoid diurnal variations. The counts were continued until the patients had recovered or until preoperative levels were established, usually within 10 to 16 days. All laboratory procedures were performed by one technician. Eosinophils were counted by the method of Wintrobe. The platelet counts were done on freely flowing capillary blood. Dilution was made with Rees-Ecker fluid and direct counting in a counting chamber was done by phase microscopy. Previous studies in this laboratory, consisting of 150 platelet counts performed by 6 technicians on 25 normal patients, show the maximum variation in platelet counts done on a single blood specimen to be 10,000 per cubic millimeter. The range of platelet counts in the 25 patients studied previously was 180,000 to 350,000 per cubic millimeter with a mean of 215,000 per cubic millimeter. Other studies on platelet changes during ovulation done in this laboratory have also indicated the reliability of this method of counting platelets. In the present study, a total of 145 platelet, eosinophil, total white counts, and differential counts were done on the 18 participating patients. The number of counts done on each individual varied from 13 to 20, depending upon the length of the operation and of the period of convalescence.

RESULTS

Platelet levels. Of the 11 patients undergoing extensive surgery, 10 patients (90.9 per cent) showed a sharp drop in platelet levels during the operative procedure or immediately following it (Fig. 1). Only 1 patient (9.1 per cent) had a rise in number of thrombocytes. The surgical thrombocytopenia varied from 25 per cent below preoperative levels in individual patients and occurred between the first hour of surgery and the fourth hour following the operation. The average decrease in platelet levels was 46.6 per cent. Platelet levels at this time varied from 40,000 to 150,000 per cubic millimeter. After the operations, the platelets remained below their preoperative values for a period of 2 to 6 days (average 3.7 days). This thrombocytopenia was followed by an interval in which the platelets rose gradually to their preoperative levels. They remained at these normal levels from 2 to 6 days (average 2.5 days).

A sudden and dramatic rise of the platelet levels occurred 3 to 10 days postoperatively (average 6.2 days). Usually the platelets became elevated during a 24 hour period to levels ranging from 36 to 150 per cent above the preoperative values. This postoperative thrombocytosis occurred in 10 patients (90.9 per cent). In some cases, values as high as 460,000 per cubic millimeter were reached. These rebound elevations of platelets lasted 2 to 5 days (average 3 days). Thereafter, a sharp drop of thrombocytes occurred, again usually within 24 hours, with the platelet levels returning to their preoperative values between the tenth and fifteenth days (average thirteenth day) postoperatively.

A platelet rise of 15 per cent above the preoperative level was noted in only 1 patient during the operation. This rise occurred during the first hour of surgery. Two hours after the procedure, the platelet levels had reached their original values. Otherwise the pattern was the same as observed in other patients.

One patient in whom postoperative thrombocytosis did not occur underwent gastric resection. The platelet levels dropped during the procedure and remained low for 7 days. On the eighth day, the platelets rose to their preoperative level. It was then necessary to do an exploratory laparotomy for obstructive jaundice. The platelet count dropped again during the second operation and remained low (100,000 per cu.mm.) until death.

The mean values as represented by the heavy line in Figure 1 give a realistic account of the acute thrombocytopenia occurring during the day of surgery, since the platelet drop occurred on the same day in 90.9 per cent of all the patients. The postoperative thrombocytosis which reached a mean peak level of 280,000 per cubic millimeter on the ninth day actually does not represent the true mean value of all peak elevations since these occurred anywhere between the sixth and thirteenth postoperative day. It only indicates the mean platelet level on that particular day.

Further analysis of these findings in relation to blood transfusions revealed that 4 out of 5 patients who were not given transfusions showed the typical picture of thrombocytopenia during surgery followed by postoperative thrombocytosis. The fifth patient had thrombocytosis of 15 per cent above the preoperative level during the first hour of surgery.

The remaining 6 patients received blood transfusions ranging in volume from 500 to 1,500 milliliters. In 3 patients surgical thrombocytopenia developed before the transfusions were started. In 2 patients the platelet levels decreased 1 hour after blood transfusions of 500 milliliters each were begun but not completed. In the sixth patient

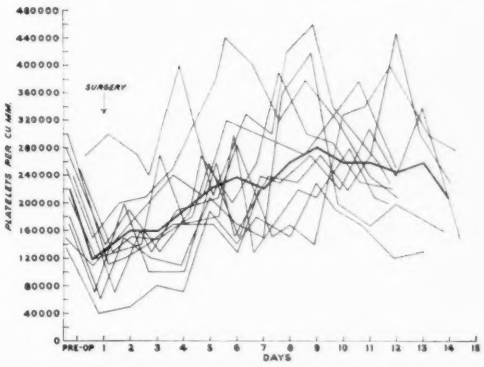

FIG. 1. Platelet levels before, during, and after operation.

who received 500 milliliters of blood during the operation thrombocytopenia developed 1½ hours after the transfusion was started and was still in progress.

Thus, in 7 patients (63.6 per cent) thrombocytopenia developed during surgery at a time when they had not received blood. Three patients (27.3 per cent) were found to have thrombocytopenia between 1 and 1½ hours after blood transfusions were begun, but before the transfusions were completed. Only 1 patient (9.1 per cent) had thrombocytosis while not receiving blood.

Comparison of preoperative platelet levels with those obtained immediately after the patients were anesthetized but before the operations were started showed no significant differences in any patients.

In the 7 patients having less extensive surgical procedures, no significant changes in platelet levels were noted.

Eosinophil levels. The preoperative levels of eosinophils in each of 10 patients subjected to extensive surgical procedures ranged from 200 to 40 per cubic millimeter (average 151 per cu.mm.). The eleventh patient was allergic, and the eosinophil count was 580 per cubic millimeter before surgery (Fig. 2).

Immediately after induction of anesthesia and before an incision was made, no changes in eosinophil numbers were noted. How-

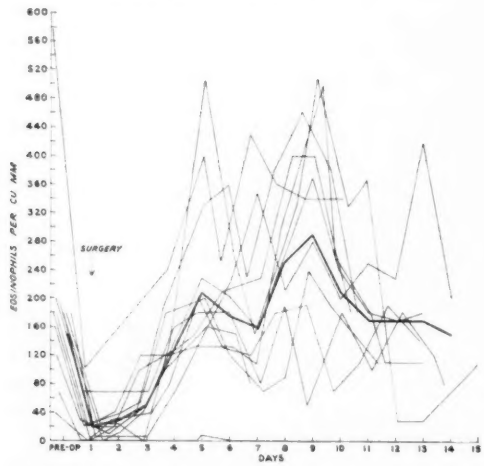

FIG. 2. Eosinophil levels before, during, and after operation.

ever, 1 hour after the operations were begun, the eosinophils gradually diminished in all patients. The lowest level of eosinophils was reached between the second hour during the operation and the third hour following it. This eosinopenia varied from 60 to 100 per cent (average 88 per cent) below the preoperative values. During this phase, the eosinophils were either absent or reached a maximum of 70 per cubic millimeter. Only in the 1 allergic patient with a preoperative level of 580 per cubic millimeter did the eosinophils drop to 100 per cubic millimeter (83 per cent decrease) during the operation.

Following surgery, the eosinophils remained low for another 24 hours, after which they rose rapidly reaching preoperative values on the fourth postoperative day. On the fifth and sixth postoperative days, a mild eosinophilia ensued, followed by a return to normal levels on the seventh day.

Between the fifth and thirteenth postoperative days (average ninth day), a pronounced eosinophilia developed, reaching peak values between 50 and 400 per cent (average 176 per cent) above preoperative levels. The eosinophils then rapidly declined to preoperative levels between the tenth to fourteenth day (average thirteenth day) after surgery.

Postoperative eosinophilia was noted in 8 patients (73 per cent). The highest eosinophil levels encountered in these patients ranged from 200 to 510 per cubic millimeter (average 371 per cu.mm.). In 2 patients, one of whom was allergic, no such rebound phenomena were observed. In the second patient, who subsequently expired, the eosinophils remained low postoperatively, never rising above 40 per cubic millimeter.

In 2 patients in whom no eosinophilia occurred, the eosinophils returned to preoperative levels in 2 and 3 days, respectively, after surgery.

The heavy line in Figure 2 indicates the mean values of the eosinophils. The sharp decrease during surgery gives a true indication of the degree of eosinopenia since all decreases occurred on the same day. The postoperative eosinophilia of 280 per cubic millimeter on the ninth day represents only the mean peak value on this day whereas the mean value of all eosinophil peaks which occurred between the fifth and the thirteenth days was 371 per cubic millimeter.

Total leucocyte levels. The total preoperative leucocyte levels of the 11 patients undergoing extensive surgical procedures varied from 5,300 to 12,000 per cubic millimeter (mean 8,750 per cu.mm.) (Fig. 3).

During the operations, the total leucocyte levels rose gradually during the progress of the procedure in all patients. This increase varied from 50 to 450 per cent (average 105 per cent) above preoperative levels. In some patients, the levels reached 24,000 per cubic millimeter. The peak levels were never maintained longer than 12 to 24 hours, when a gradual decrease began. On the second and third postoperative days, about equal numbers were maintained. On the fourth postoperative day, the total leucocytes were 22 per cent above normal. From the fifth day on, preoperative values were reached again, and were maintained until the patients recuperated completely. This typical leucocyte picture was observed in all patients except in the 1 who expired and

in whom the total leucocyte numbers remained high until death. No infection was present.

In 7 patients (63 per cent), the leucocytes returned to normal on the fifth postoperative day. In 1 patient, the return to normal occurred on the seventh day and in 2 patients on the eleventh postoperative day. It was observed that in 7 patients (63 per cent), the decrease in leucocytes to normal levels occurred during a 24 hour period, and coincided with the rebound elevation of the platelets.

The heavy line in Figure 3 indicates the mean values of total leucocytes in all periods during and after surgery.

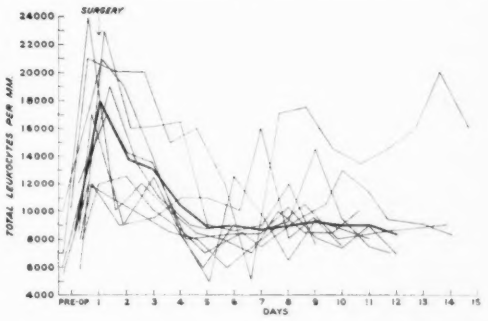

FIG. 3. Total leucocytes before, during, and after operation.

DISCUSSION

The characteristic response of the circulating platelets to the trauma of extensive surgical procedures was a sudden thrombocytopenia which developed during the operation or within the following 4 hours. After the platelets returned to their preoperative levels on the fifth postoperative day, no appreciable changes were noted until the seventh postoperative day when a sudden thrombocytosis developed and persisted for an average of 6 days. The platelets then returned to their preoperative levels where they remained thereafter.

We were unable to confirm completely the findings and to agree with the conclusions drawn recently by Mustard who reported thrombocytosis during and following extensive operations. He concluded that surgical thrombocytopenia was caused by blood transfusions. On the contrary, in 7 patients (63.6 per cent) in the present study pronounced thrombocytopenia developed during surgery although they did not receive blood. Or if they were transfused, the platelet decrease occurred before the blood was actually administered. In 3 patients (27.3 per cent) in whom thrombocytopenia occurred while the blood transfusions were still in progress, it seems unlikely that the 500 milliliters of blood administered could have sufficiently diluted the recipient's platelets to produce thrombocytopenia of 35 to 50 per cent below the preoperative levels as was encountered in these patients. Only 1 patient (9.1 per cent) had thrombocytosis during the surgery which lasted 1 hour, while not receiving blood.

Our findings of marked surgical thrombocytopenia agreed with those reported by Warren and associates. The postoperative thrombocytosis was essentially the same as observed by others.

CAUSES OF SURGICAL THROMBOCYTOPENIA AND POSTOPERATIVE THROMBOCYTOSIS

Many theories have been advanced seeking to explain surgical thrombocytopenia and postoperative thrombocytosis. Dawbarn and associates and Pohle offered the explanation that postoperative thrombocytosis was caused by absorption of necrotic material or exudate from wounds. Warren and associates believed that stress of the operative procedure was responsible for the surgical thrombocytopenia, but had no explanation for the postoperative thrombocytosis. He was able to duplicate the surgical thrombocytopenia by administration of corticotropin but did not find an ensuing thrombocytosis. Zucker stated that a demand for platelets in the operative wound, needed for hemostasis in the smaller blood vessels, was one factor causing the decrease in platelet levels in the early postoperative period.

It has been demonstrated repeatedly that

surgical trauma causes a release of corticotropin from the anterior lobe of the pituitary gland, stimulating increased secretion into the plasma of 17-hydroxycorticosteroids (17-OHCS) by the adrenal cortex. The preoperative level of 17-OHCS has been reported to average 5.6 micrograms per cent by Franksson and associates. This level increased to an average of 31.4 micrograms per cent during the first hour of surgery. The acute rise of 17-OHCS lasted for 24 to 72 hours (average 38 hours). Steenburg and associates reported a similar pronounced rise of 17-OHCS lasting 48 hours after extensive surgical procedures.

In concurrence with these findings, we noted that the eosinophil levels decreased rapidly with the progress of the operations, either reaching very low levels or disappearing altogether in a few patients. The eosinophils remained at these levels for an average of 3 days, and then returned to their preoperative values. Platelet levels dropped simultaneously with the eosinophils and maintained low levels for an average of 3.7 days, after which they too returned to their preoperative numbers. Thus, both the eosinophils and platelet levels had returned to preoperative values by the fourth postoperative day. It was also on the fourth day that Franksson and associates reported the 17-OHCS to return to levels slightly below the preoperative values. On the fifth day the 17-OHCS were slightly above the preoperative levels and here they remained for an average of 3 days.

On the seventh postoperative day in the present study, a sudden eosinophilia developed lasting for an average of 4 days, after which the eosinophils returned to their preoperative levels. Paralleling this sudden rise of the eosinophils, the platelets rebounded similarly and remained at high values for an average of 3 days when they too returned to normal numbers. Thus a close, parallel, wave-like pattern of fluctuating platelet and eosinophil levels existed from the beginning of the period of surgical stress to its conclusion (Fig. 4).

The postoperative eosinophilia might suggest a temporary decrease in production of 17-OHCS caused by diminishing stress, decreased demand on the pituitary gland, or a decreased adrenocortical response. However, a relationship between eosinophilia and 17-OHCS levels was not established by the studies of Franksson and associates who did not find a postoperative eosinophilia, and who reported normal 17-OHCS levels beginning on the sixth postoperative day. These investigators concluded their observations on the eighth postoperative day and presumably missed the eosinophilia often occurring as late as the tenth to twelfth postoperative days.

Steenburg and associates reported postoperative eosinophilia in 40 per cent of their patients. They noted "a much closer inverse correlation with the reduction in urinary excretion curve of total 17-OHCS than with the fall in blood concentration curve of the free steroids." Analysis of their cases, however, shows that daily eosinophil and steroid levels were only done in 1 patient, whereas in the others these determinations were carried out only every second or third day. It is possible that higher values of eosinophils and lower levels of steroids might have been found if the determinations had been done more frequently, since peak values of eosinophils in the present study usually persisted for only 24 hours.

The close relationship between the circulating eosinophils and the fluctuating plasma steroid levels has been recognized in normal individuals. Because of the parallel fluctuating levels of both eosinophils and platelets during and following major operations, it appears likely that postoperative thrombocytosis, like postoperative eosinophilia, may be responses to the same governing mechanism, namely hypoactivity of the adrenal cortex following its hyperactivity during stress.

Response of eosinophils before and during surgical procedures. The changes in levels of the circulating eosinophils during and after surgery is well known. The fluctuating

eosinophil levels are an index of the activities of the adrenal cortex. We have noted that with the approach of the day of surgery, the level of eosinophils gradually decreased in numbers. There is considerable evidence that stressful emotional situations can stimulate the adrenal cortex and increase the excretion of 17-ketosteroids and 17-OHCS and also cause a rise in 17-OHCS in the plasma.

In 2 of the 10 nonallergic patients, very low eosinophil counts were noted preoperatively numbering 40 and 70 per cubic millimeter, respectively. It was believed that in these patients these low levels were probably due to preoperative painful conditions. After induction of anesthesia with sodium pentothal and nitrous oxide, no changes in levels of eosinophils were observed. The decrease in eosinophils began within the first few hours after the operation was concluded. In general, no relationship existed between the severity of the operation and the degree of eosinophilia. It was interesting to note that when postoperative eosinophilia finally occurred, the majority of the patients expressed a feeling of improvement and well-being. This finding would again suggest a diminution of stress, a relative decrease in production of corticosteroids, and hence, an eosinophilia.

Response of total leucocytes to surgery. With the beginning of the surgical procedure, the total leucocytes rose quickly, but these high levels were never maintained for more than 12 to 24 hours. No relationship between the levels of total leucocytes or the rapidity of their return to normal and the magnitude of the operations could be established. For instance, patients with a gastric resection and an arthrotomy each showed a 50 per cent increase in total numbers of leucocytes, and each showed a return to normal on the fourth postoperative day. Two patients having colectomies done by the same surgeon in approximately the same time and having similar postoperative courses and results showed a 100 per cent operative leucocytosis in one case and 400 per cent surgical leucocytosis in the other. In the patient who had a rise of 400 per cent the total leucocytes returned to normal on the fourth postoperative day, whereas the patient with the leucocytosis of 100 per cent had a normal white blood cell count on the eleventh postoperative day.

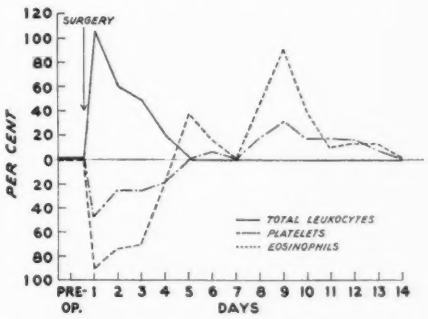

FIG. 4. Percentage changes of platelets, eosinophils, and total leucocytes during and after operation.

In 50 per cent of the patients, the white blood cells returned to preoperative levels on the same day (the seventh postoperative day) when the platelets and the eosinophils rebounded to their high postoperative values. In the remainder of the patients, normal leucocyte levels were regained on the third, fourth, or eleventh postoperative days.

Differential counts showed a short lasting absolute increase of the neutrophilic leucocytes and an absolute decrease of the lymphocytes during surgery.

Postoperative venous thrombosis. In this study, thrombocytosis usually developed on the third to tenth postoperative day during a 24 hour period which coincides with the time when postoperative venous thrombosis is usually encountered. The meteoric rise of the platelets to 200 per cent above preoperative levels in some instances, associated with pre-existing endothelial damage and diminished circulation, may well explain the development of postoperative thrombosis. None of the patients in this study, however, had evidences of postoperative venous thromboses, since they were ambulatory early postoperatively.

Interrelationship of platelets, total leucocytes,

and eosinophils during and after surgery. During the surgical procedures, the total leucocytes increased rapidly to an average of 105 per cent above preoperative levels (Fig. 4). At the same time, the eosinophils decreased to an average of 88 per cent and the platelets dropped 46 per cent below preoperative values. All these blood elements returned gradually to preoperative numbers by the fifth day. Whereas the levels of leucocytes remained normal thereafter, the platelets and eosinophils showed marked increases by the eighth day, and reached maximum heights on the ninth when the platelets averaged 29 per cent and the eosinophils 88 per cent above preoperative levels. Both returned to their preoperative values by the fourteenth postoperative day.

CONCLUSIONS

1. Platelet, eosinophil, total leucocyte, and differential counts were performed on 18 patients before, during, and after extensive and less extensive operations. Leucocytosis appeared during the day of surgery and the total leucocytes returned to normal levels by the fifth postoperative day. The platelets and eosinophils showed a pronounced decrease during and immediately after extensive operations, followed by a short period of normal values. A sudden thrombocytosis and eosinophilia then ensued, after which normal preoperative levels were re-established.

2. Because of the simultaneous and similar behavior of both the eosinophils and the platelets after extensive operative procedures, it is suggested that these responses resulted from the varying reactions of the pituitary-adrenal axis to surgical stress.

3. No significant changes in these blood elements occurred during or after less extensive surgical operations.

4. Postoperative venous thrombosis may be the result in part of the sudden and pronounced thrombocytosis.

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THE SURGICAL CONSIDERATIONS OF 258 PATIENTS WITH CAROTID ARTERY OCCLUSION

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CAROTID ARTERY THROMBOSIS in the neck was sporadically discussed in the literature before 1950 by Andrell, Kussmaul, Moniz, Penzoldt, Sjoqvist, Wolfe, and others. We reported on thrombosis of the carotid bifurcation before the American Neurological Association in 1949 (6). The important article by Fisher on occlusion of the internal carotid artery in the neck, based on necropsy material, appeared in 1951.

With greater interest in angiography, more and more cases of cervical carotid artery diseases were encountered. It was soon discovered that internal carotid artery occlusion in the neck was much more common than occlusive diseases of the entire bifurcation. In 1953, we (7) reported upon 30 patients with stroke syndrome associated with internal carotid artery thrombosis in the neck. By 1956, we had collected 70 examples (15).

Because of greater interest in cerebrovascular disease and careful angiographic delineation of carotid vessels in the neck, partial occlusions were soon recognized. Such cases presented the possibility of surgical treatment by endarterectomy. The studies of dosSantos, Eastcott, Pickering, and Rob, as well as others led the way. Recently, DeBakey, Crawford, Cooley and Morris, Lyons and Galbraith, and Murphey and Miller have reported their experience with large numbers of cases in which endarterectomy and/or bypass operations were performed. The importance of occlusive diseases of mediastinal vessels in the stroke syndrome was emphasized.

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Aided by a grant from the Kresge Foundation.

In any disease process, a careful evaluation of the pathologic lesions responsible for the various clinical manifestations results in sound principles of management. Only then do the different methods take their rightful place in the treatment of the disease.

MATERIAL

From September 1948 through May 1959, we examined 258 patients with carotid artery occlusion in the neck, proved either by angiography or by surgical exploration. Complete and partial occlusions are included in this study. One-hundred eighty of these patients were male, 78 were female. In Table I, figures on the age distribution in these groups are given. It may be seen that the majority, 193 patients, were in the 51 to 70 age groups.

Symptoms and signs in these cases varied from sudden or apoplectic at onset to episodic with recurring focal abnormalities. In a certain number of cases, the complaints were progressive, simulating a mass lesion. Other patients had only minor symptoms of a nonfocal character; these included headache, dizziness, nervousness, difficulty in concentration, and other minor complaints which may be premonitory symptoms, not only of this condition, but of many other illnesses. In 131 cases of complete occlusion, the type of onset was as follows: sudden 70, episodic 37, progressive 17, and minor 7. Among the 127 cases of partial occlusion the onset was sudden in 49 cases, episodic in 43, progressive in 17, and minor in 18.

Among the 258 cases of carotid artery occlusion, there were 131 patients with complete occlusion of the internal carotid artery; in 53 patients the occlusion occurred

TABLE I.—AGE DISTRIBUTION

Admittance group, yrs.	*No. patients*	*Per cent of total*	*No. expired*	*Per cent of total*	*Per cent of age group expired*
		COMPLETE THROMBOSIS*			
Under 41	6	4.6	—	—	—
41 to 50	18	13.7	5	8.6	27.8
51 to 60	53	40.5	26	44.8	49.
61 to 70	40	30.5	19	32.8	47.5
71 to 80	14	10.7	8	13.8	57.1
Totals	131		58		44.3
		PARTIAL THROMBOSIS**			
Under 41	1	.8	—	—	—
41 to 50	4	3.2	—	—	—
51 to 60	49	38.6	9	29	18.3
61 to 70	51	40.1	16	51.6	31.4
71 to 80	22	17.3	6	19.4	27.2
Totals	127		31		23.6

*Male: 100 (Negro 4); female: 31 (Negro 2)
**Male: 80 (Negro 3); female: 47

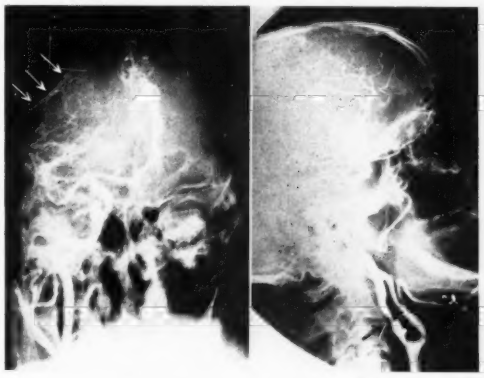
on the right side, in 69 on the left side, and in 9 bilaterally. The siphon area was involved in 11 instances. Among these 131 cases, there was complete occlusion on one side and partial occlusion on the other side in 7 cases; and the entire carotid bifurcation was occluded in 5 instances. Three cases involved the common carotid in the mediastinum.

Partial occlusion of the internal carotid artery was seen in 127 patients, with right-sided involvement in 46, left-sided in 34, and bilateral stenotic lesions in 47. As experience is gained in angiographic studies, partial occlusions of the internal carotid artery are being diagnosed more frequently because of the increased attention given to the bifurcation area. Partial occlusions appear to be frequent. In our earlier studies, undoubtedly, many cases of partial occlusion of the internal carotid artery were missed or overlooked. In some instances, the partial occlusion may have been a concomitant finding with other intracranial disease. In these instances, it was not clear whether the stenosis contributed to the clinical findings since, on occasion, it was associated with brain tumor, subdural hematoma (Fig. 1), and other mass lesions. Partial occlusions were also seen in association with aneurysms, intracranial hemorrhage, and brain infarction. In some cases, partial occlusion may be found on the same side as the weakness of the body. It is difficult to say whether, in such cases, it is merely an incidental finding, or whether it is significant by virtue of a lowered total blood flow to the brain, so that with bouts of low blood pressure an area of infarction or ischemia may occur on either side, or that plaque formation may not contribute to embolic phenomena.

In 1 of our recent cases of stenosis of the right common carotid artery near the innominate, a rupture of an aneurysm of the arch of the aorta and the innominate artery was the cause of death. This patient had been seen 2 years earlier and at that time there was hemiplegia of the left side. Compression of the left bifurcation resulted in syncope, but bilateral angiograms at that time did not reveal any pathologic change in the carotid bifurcation or in the intracranial vessels. The paralysis subsided, and the patient was discharged. A roentgenogram of the chest at this particular time revealed some irregularities of the aortic arch near the innominate artery. He was rehabilitated and for 2 years his condition was satisfactory. On several occasions, compression of the left carotid bifurcation resulted in syncope. His blood pressure was 180 to 190 over 100 to 105. A few days before he entered the hospital, there had been a death in the family which caused serious emotional difficulties. He suddenly became comatose, was hospitalized, and died within 18 hours. Evidence of some weakness of the left half of the body and a positive plantar reflex were noted. Autopsy revealed partial occlusion of the common carotid artery due to a hemor-

TABLE II.—SURGICAL PROCEDURES IN 258 CASES

	Cases	*Arteries*
No. patients operated upon 111 plus 7 craniotomies (1 also had carotid artery exploration)	117	
No. arteries operated upon		115
Excision for complete occlusions (sympathectomy in 31 cases, 33 arteries)	71	73
Endarterectomy for complete occlusions	8	8
Retrograde flow obtained 2		
No retrograde flow obt'd. 6		
Sympathectomy 5		
Circulation restored 1		
Endarterectomy for partial occlusions	22	23
Retrograde flow obtained 22		
Sympathectomy 6		
Circulation restored 17		
Others		
Arterial anastomosis	1	1
Thrombectomy	1	1
Exploration only (sym. 4)	7	7
Graft after endarterectomy		1
Left vertebral exploration	1	1
Total No. arteries operated upon	115	
Total sympathectomies	48	
Total craniotomies	7	
Total operations	122	



a b

FIG. 1. R. B., aged 57. a, Large subdural hematoma may be seen over right parietal region. b, Lateral angiogram shows marked narrowing of the right internal carotid at bifurcation. This patient had syncope on compression of the left carotid bifurcation. Removal of hematoma resulted in complete disappearance of symptoms which were headaches and weakness on the left side, with no complaints for the past 3½ years.

rhage which dissected the intimal lining from the media at the point where the common carotid artery branched off the innominate. There was also an aneurysmal rupture of the innominate and aortic arch junction. Study of the brain showed an area of infarction in the internal capsule on the right side. This was an old infarct which had resulted from an illness 2 years previously when there was hemiplegia of the left side. The area of infarction, about 4 by 8 by 3 millimeters in size, may be seen in Figure 2. The initial left-sided hemiplegia was accountable to the infarct area in the right internal capsule. This may have resulted from forward embolism from the aortic-innominate aneurysmal dilation with mural clotting.

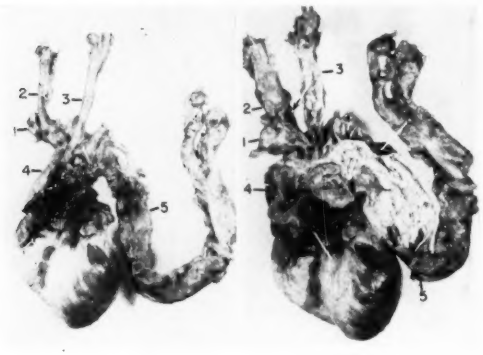
Among those patients with bilateral involvement, complete occlusion on one side and partial occlusion on the other were noted in 7 instances. These patients present an interesting problem, as do the 9 cases of complete bilateral occlusion. Bilateral partial occlusions were seen in 47 examples.

CLINICAL FINDINGS

Initial unconsciousness in the apoplectic form of onset of this disease was noted in 28 cases. There was a high incidence of both disability and mortality in this group. Fourteen of 28 of these patients died within 2 weeks after onset of illness. In the surviving patients, there were varying degrees of motor disability and frequent severe speech disturbance when the left carotid was involved. In this group, the inadequacy in the blood flow to the brain on the side of the occlusion from lack of proper collateral circulation may have been the cause of the unconsciousness as well as of the severe morbidity. The latter was frequently associated with obvious infarction of the brain in autopsied cases.

Nineteen patients in this study had convulsions; there were 5 cases of grand mal seizures and 10 jacksonian seizures with complete occlusions. Among those with stenotic lesions who were operated upon, there were 2 patients with grand mal and 2 with focal seizures. Jacksonian seizures should not be confused with focal cerebral abnormalities, such as a feeling of numbness in an extremity, or a feeling of weakness which may persist for varying periods of time.

Among the minor complaints in 52 patients were recurrent attacks of dizziness or



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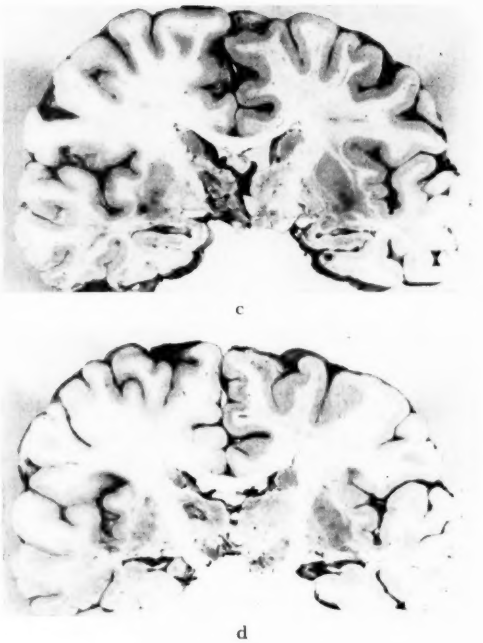


c d

FIG. 2. a and b, *1*, Right subclavian artery; *2*, right common carotid artery; *3*, left common carotid artery; *4*, aorta; *5*, descending aorta. Arrow shows hemorrhagic extravasation compressing the common carotid at its origin from the innominate artery. c and d, Cross sections of the brain showing area of old infarction involving right internal capsule and anterior thalamus. Note that basal nuclei on the right are atrophied when compared with the left.

momentary syncope, usually not associated with falling. The blood pressure in 116 patients was 150/90 and above, indicating a degree of hypertension, shown in about half of the total number of cases.

Dull generalized headaches, a feeling of pressure in the head and neck, or occasionally severe bursting pains in the head were noted in 15 per cent with carotid occlusion.

Hemiplegia or hemiparesis was noted in 131 patients. In 11 patients there was focal weakness, more severe in the upper limb, on one side of the body. In this group, also, some degree of sensory loss was noted. Tetraplegia was observed in 1 instance.

Among 22 patients, there was no paralysis nor had there been any history of paralysis. Among this group, 19 patients had complete occlusion of one internal carotid artery with minimal complaints. The possibility of thrombosis of the internal carotid artery in the neck was considered only when compression of the opposite carotid resulted in a syncope, or when a diagnostic angiogram showed an occlusion of the carotid artery.

Homonymous hemianopsia was found in 6 cases. In 4, there was complete, in 2 partial occlusion. There were 3 cases of optic atrophy with blindness. Complete ophthalmoplegia on the right occurred in 1 case.

SURGICAL TREATMENT AND PROGNOSIS

The various surgical procedures performed in 258 patients with carotid occlusion are given in Table II. In many instances at operation, complete occlusion of the internal carotid artery was noted and, on exploration, there was no bleeding from the distal end. In such cases, excision of a portion of the carotid artery and a cervical sympathectomy were performed. In a certain number of complete occlusions, the process appeared to be quite fresh, and an effort was made to restore retrograde flow by sucking out the clot from the internal carotid artery at the base of the skull. In 2 out of 8 cases, retrograde flow was obtained, and, in 1 of these, circulation was apparently restored as evidenced by the angiograms made 2 months later.

TABLE III.—FOLLOW-UP OF 131 CASES OF COMPLETE CAROTID OCCLUSION

	Type of onset				*Results*				
Condition of patient when first seen	*Sudden*	*Progressive*	*Episodic*	*Minor complaints*	*Working*	*Walking*	*Wheel chair*	*Bedfast*	*Deaths*
Acutely and severely ill, 31 cases	24	3	4	0	4	5	4	18	
	13*	2*	2*		1*		2*	14*	17
Moderately ill, 49 cases	31	7	11	0	5	24	8	12	
	14*	5*	6*			10*	6*	9*	25
Chronically ill, 51 cases	15	7	22	7	16	25	6	4	
	5*	2*	8*	1*	1*	9*	5*	1*	16

*Dead

TABLE IV.—RESULTS IN 83 PATIENTS WITH COMPLETE CAROTID OCCLUSION OPERATED UPON, EARLY AND LATE

	Type of onset				*Results*				
Condition of patient when first seen	*Sudden*	*Progressive*	*Episodic*	*Minor complaints*	*Working*	*Walking*	*Wheel chair*	*Bedfast*	*Deaths*
Acutely and severely ill, 17 cases	16	1	0	0	2	3	3	9	
	7*	1*			1*		1*	6*	8
Moderately ill, 30 cases	22	4	4	0	4	13	6	7	
	7*	2*	2*			3*	4*	4*	11
Chronically ill, 36 cases	9	5	19	3	10	21	5	0	
	3*	2*	7*			7*	5*		12

*Dead

TABLE V.—RESULTS IN 48 PATIENTS WITH COMPLETE CAROTID OCCLUSION—NO OPERATION

	Type of onset				*Results*				
Condition of patient when first seen	*Sudden*	*Progressive*	*Episodic*	*Minor complaints*	*Working*	*Walking*	*Wheel chair*	*Bedfast*	*Deaths*
Acutely and severely ill, 14 cases	8	2	4	0	2	2	1	9	
	6*	1*	2*			1*(4 yrs.)	1*	8*	9
Moderately ill, 19 cases	9	3	7	0	1	11	2	5	
	7*	3*	4*			7*	2*	5*	14
Chronically ill, 15 cases	6	2	3	4	6	4	1	4	
	2*		1*	1*	1*	2*		1*	4

*Dead

Surgical treatment for complete occlusion consisted of excision of a portion of the artery in 71 instances and an associated superior cervical sympathectomy in 31 of these 71 cases. The rationale for the excision of the portion of artery was that reducing the pulsatile force of the heart upon the vessel would thereby minimize the possibility of dislodgment of a portion of the clotted material at the upper end of the occluded vessel and prevent forward embolism. Sympathectomy may help to increase the extracranial blood flow with the hope that some will reach the intracranial vessels through communications at the base of the skull or the frontal-ophthalmic collaterals. Such communications are often demonstrated in angiographic studies.

Intimectomy for complete occlusion was performed in 8 cases. Retrograde flow from the distal portion of the vessel was obtained in 2 instances. In 1 of these cases, an angiogram made 2 months later revealed that the vessel was functioning. In the other case of retrograde flow, an angiogram taken 22 days postoperatively showed the vessel to be completely closed. This patient recovered from the hemiparesis but administration of anticoagulants was continued. He is a full time preacher now, 26 months after operation. Two of the 8 patients died; one, who was moribund from the onset, on the third postoperative day, and the second died 6 months postoperatively without recovery from the severe hemiplegia. The remaining 4 in this group without retro-

grade flow recovered to the wheel chair state.

The 131 cases of complete occlusion of the internal carotid artery which were followed up are analyzed in Table III. Thirty-one patients were acutely and severely ill when first seen, 49 were moderately ill, and 51 were chronically ill for many weeks or months. The nature of onset is also indicated in the tabulation. It should be noted that in a great many patients onset was sudden with a single attack resulting in disability. There were 70 examples of sudden onset, 17 instances of progressive symptomatology, and 37 examples of episodic abnormalities. There were 7 cases of minor complaints of nonfocal nature. Twenty-five of the entire group were able to return to work for varying periods of time, 54 improved sufficiently to walk, even though some had a definite hemiplegic gait, with or without speech disturbance, depending upon the side involved. Eighteen were confined to wheel chairs and 34 were bedfast. Among the working group, 19 patients had minimal disabilities,[1] 5 had moderate disabilities, and 1 had no disability. Among those who could walk, the disability was minimal in 14, moderate in 31, and severe in 9. The disability of those patients confined to wheel chairs was considered moderate in 8 and severe in 10. In the bedfast patients, disability was moderate in 5 patients and severe in 29. Those classified as able to walk could have worked if they had been younger and had not been superannuated.

Table IV shows the results in 83 patients operated upon in whom excision of a portion of the artery, intimectomy, exploration, thrombectomy and/or sympathectomy were carried out. Table V is an analysis of 48 patients in whom the only operative intervention was an angiogram. Although the cases listed in these tabulations are not comparable, it is rather interesting to note that those patients who had operative intervention fared somewhat better—64 per cent working and walking—than those who refused operation or were moribund and, therefore, were not operated upon—52 per cent working and walking. This result may have been due in part to the interest shown these patients not only by the operative intervention but also by the rehabilitative and other measures instituted after treatment.

The type of onset and findings in 127 cases of partial occlusion have already been discussed. Among the 127 partial occlusions there were 38 associated with other vascular lesions and concomitant disease processes as follows: anterior cerebral artery occlusion in 9 cases, middle cerebral artery occlusion in 4, arteriovenous malformation in 1, intracerebral hematoma in 3, right anterior and left middle cerebral artery occlusion in 1, subdural hematoma in 1, basilar-vertebral artery disease in 2, generalized cerebral arteriosclerosis in 4, trigeminal neuralgia in 1, vertebral artery occlusion in 1, middle cerebral arteriolar disease in 8, subarachnoid hemorrhage in 1, left vertebral occlusion and anterior cerebral occlusion in 1 (left vertebral artery explored), and right parasagittal meningioma (Fig. 3) in 1. As previously stated, it is difficult to ascribe clinical importance to carotid stenosis in the presence of an associated condition which, when treated, results in symptomatic cure. Subdural hematoma, in association with a right carotid bifurcation stenosis, was surgically removed and the patient had complete freedom from symptoms for a period of 3½ years (Fig. 1). The cause and effect relationship between the stenosis and the clinical findings cannot be denied in many cases. In this group of 127 partial occlusions, 25 patients were operated upon for relief of the stenosis, 22 had intimectomy, and 1 had the scar from a postthyroidectomy removed to repair the deforming stenosis of the carotid bifurcation (Fig. 3). In 1 case,

[1]The degree of disability has been graded on the basis of: none, no history of paralysis or speech disturbance, normal neurologic findings; minimal, history of paralysis and/or dysphasia with marked improvement and minimal neurologic deficits; moderate, persisting weakness of one-half of the body with upper extremity preponderance, dysphasia with left-sided lesions; severe, severe hemiplegia and/or aphasia with or without mental abnormalities.

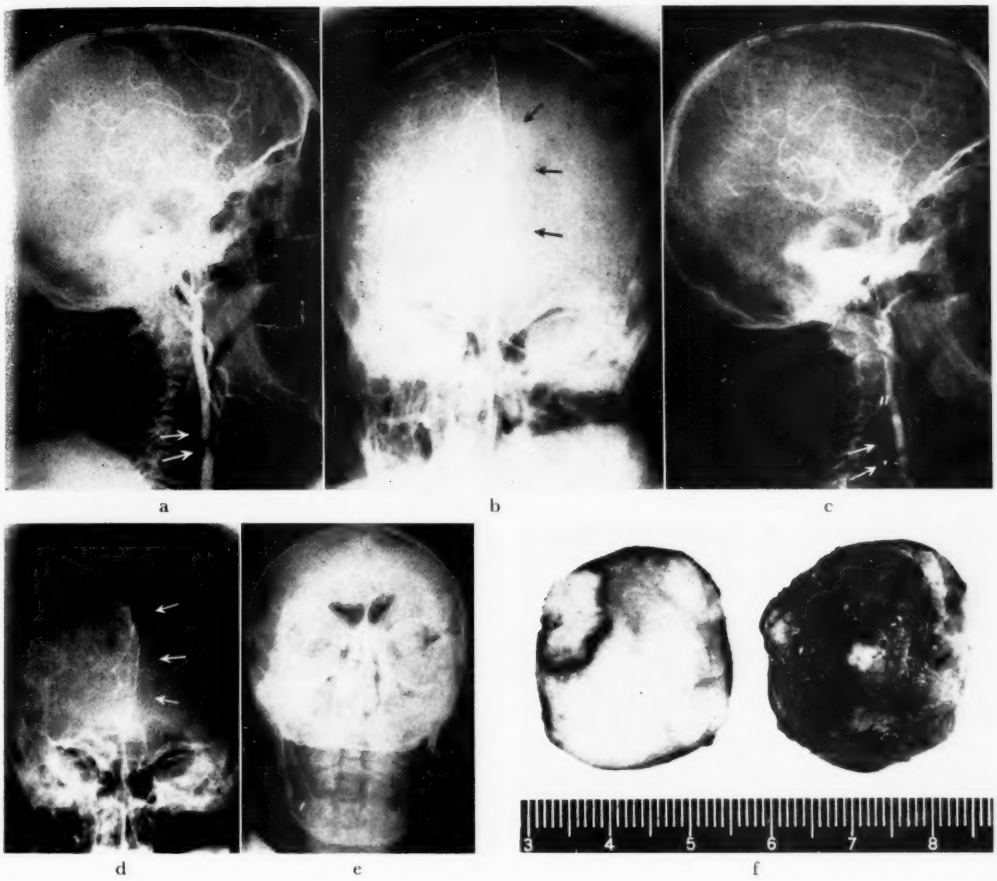
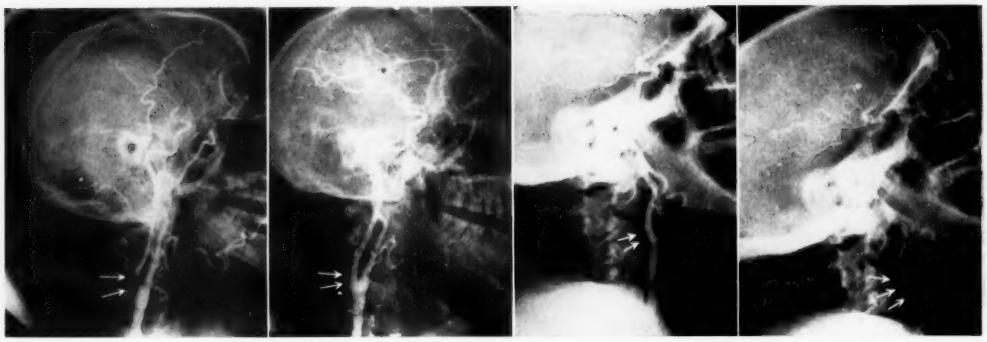


FIG. 3. a, J. K. had left-sided weakness of the face, mainly, associated with right carotid bifurcation stenosis. b, Anteroposterior view shows bulging of the anterior cerebral to the left. This was thought to be due to a swelling of the brain. At operation, a scar from thyroidectomy appeared to deform the vessel. The patient recovered completely. He returned 8 months later with recurrent left-sided symptoms and stupor. c, The angiogram at this time showed a minimal deformity of the bifurcation and a more marked shift of the anterior cerebral (d). e, Air study shows a parasagittal mass. f, A right parasagittal meningioma was removed and the patient recovered from coma and hemiparesis.

the external carotid was anastomosed with the internal carotid, bypassing the stenosis; in another the artery was ligated.

An analysis of 22 patients with intimectomy for stenosis of the carotid artery is given in Table VI (Fig. 4). The technique of intimectomy has been described previously (8). In this group of 22 patients, 23 arteries were operated on, since there was 1 instance of bilateral stenosis. Twenty-four operations were performed which included 1 nylon graft for aneurysmal dilatation after intimectomy, done by our colleague Herbert Robb. Severe disability characterized by paralysis of one-half the body with or without aphasia was noted in 9 patients. Of these, 1 had bilateral partial occlusion with involvement of the left cerebral hemisphere, and 3 had been moribund from the beginning. Thirteen patients had



a b c d

FIG. 4. a and b, E. R. before and after endarterectomy of the right internal carotid artery. Endarterectomy done January 9, 1958 and repeat angiogram made on March 25, 1958. c and d, M. J. before and after endarterectomy of right carotid artery, December 1, 1958, and repeat angiogram taken February 18, 1959.

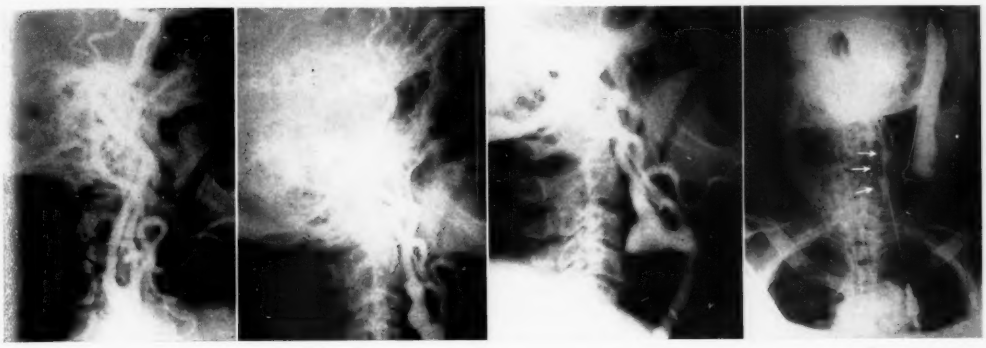
minor focal disability, or their disability had partially disappeared at the time of surgery. Among the 9 patients with severe disability following stroke, the vessel was patent 1 month after endarterectomy in 1 patient, but paralysis never subsided and death ensued 10 months later. In another patient, the vessel was found to be open at the end of 1 month, but this patient also died 3 months later. In a third, the vessel was found to be open 3 months after endarterectomy, but 8 months later paralysis recurred, and the vessel was found to be completely closed at autopsy. One patient died during endarterectomy. There has been some improvement in the clinical status of 5 other patients in this group in which the vessel was found to be working at completion of operation, although additional angiograms were not made.

In the group of 13 patients who had little or no disability at the time of operation, 1 expired 1 day after operation, and autopsy was not performed in this case. Another patient is working full time 26 months after operation. No postoperative angiogram has been obtained in this instance. In a 42 year old male in whom recovery from right-sided weakness and motor aphasia was complete, an angiogram taken 8 months later showed the left internal carotid artery to be completely occluded. Two other patients in whom vessels had closed 2 and 8 months afterward, respectively, are apparently well and working every day. In another patient (Fig. 5), the vessel has been patent for about 21 months. Some aneurysmal enlargement at the site of the intimectomy made it desirable to use a nylon graft in this region. In 17 patients with 18 intimectomies, the 18 arteries were patent.

Among the 22 patients with intimectomy, 7 expired. Death came to 3 of the 7, 8 months, 10 months, and 15 months postoperatively. One died at operation, another, 1 day, another, 2 days, and another, 4 days postoperatively.

TABLE VI.—ANALYSIS OF 22 PATIENTS WITH INTIMECTOMY FOR STENOSIS OF THE CAROTID ARTERY

	No.	
Arteries operated upon (1 bilateral)		23
Operations (1 nylon graft for aneurysmal dilatation after intimectomy)		24
Vessels open at end of operation or later (1 bilateral)		16
Repeat angiograms done 1 to 21 mos. postoperatively	7	
Open according to angiogram 3 mos. postoperatively but closed at autopsy 5 mos. later	1	
Open according to angiogram at operation or had retrograde flow	7	
Vessels closed		5
In 1 week	1	
Open to siphon at operation	1	
In 20 days	1	
In 2 mos.	1	
In 8 mos.	1	
Not checked by angiography		2



a b c d

FIG. 5. a, L. D., arrow shows partial occlusion of the left internal carotid artery. b, Angiogram taken July 29, 1957, after endarterectomy performed on June 28, 1957. Some dilatation of the bifurcation can be noted. c, Angiogram taken April 2, 1959 shows aneurysmal dilatation of the bifurcation on the left. d, Excision of the aneurysmal dilatation and repair with nylon graft, April 2, 1959.

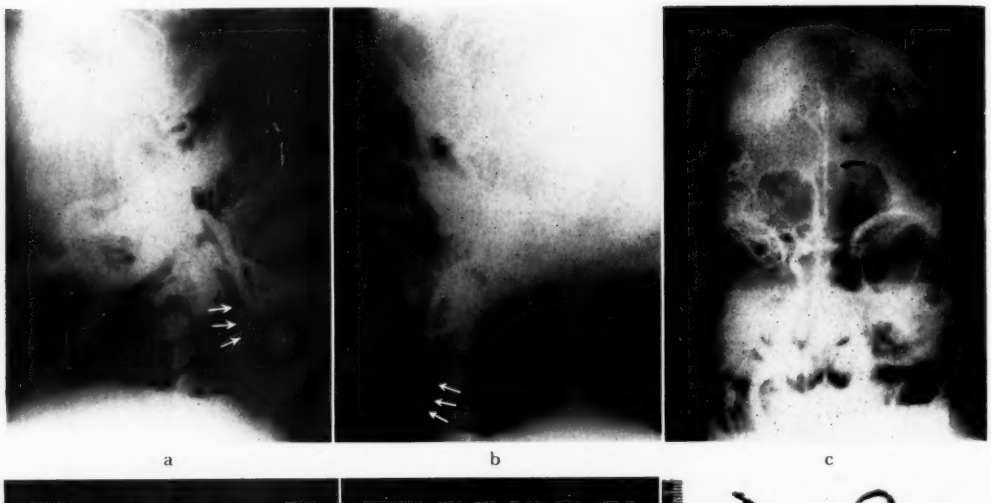
The treatment of those who were moribund or very ill with severe disability at admission is fraught with many difficulties, and many of these patients did not do well, even after circulation was re-established. In 3 of 22 patients, death may be said to have been postoperative. One with little or no disability at the time of admission belonged in this class; the other 2, however, were severely ill from the beginning.

Although it would be extremely desirable to treat partial occlusions before serious damage has been caused, in a certain number, even with partial occlusion, serious damage has already occurred at the time of the first examination, or with the first attack of the disease.

DISCUSSION

Since the brain receives its blood supply through four channels, two carotids and two vertebrals, it can forego the need for patency of any one of the four channels, provided that the collateral circulation, either in the neck or at the base of the brain, is adequate. Thus, one can get along satisfactorily if only one carotid is tied off and, in an occasional case, the patient has done well with both carotids sacrificed. The latter situation has been encountered either in spontaneous carotid occlusion on both sides, or in instances in which one carotid and then the second had to be ligated for arteriovenous communication between the carotid and the cavernous sinus.

It is quite apparent, therefore, that a carotid may be sacrificed in the management of aneurysms of the internal carotid artery. In those instances in which a carotid ligation is found desirable, it has been shown that if the carotid artery can be completely occluded for 5 to 10 minutes, this vessel can then be ligated, and in more than 90 per cent, such ligation would be successful and without any untoward effects. The same, therefore, would be true if, in doing an intimectomy, one were able to clamp the internal carotid artery feeding the brain for a period of more than 5 minutes. That such a vessel could be sacrificed without too much strain on the brain economy, is well founded. The reasons for doing an intimectomy on a patient whose internal carotid artery can be ligated for good and without danger to the patient in the proximate future are twofold. First, an additional path for blood to be transported to the brain is some insurance against the possibility that the other three vessels may also be involved. Secondly, the presence of a partial obstruction may either be associated with forward embolism or it may lead to ischemia and brain infarction



a b c

d e f

FIG. 6. a and b, Angiograms of P. G. showing bilateral carotid bifurcation stenosis. c, Anterior cerebral is seen in the midline. Patient had bloody cerebrospinal fluid, paralysis in the right half of the body, and total aphasia and a history of numbness in the left half of the body 1 year earlier. Ten days after admission, he expired after a massive intraventricular hemorrhage in the right hemisphere. d, Old hemorrhagic infarction in the left hemisphere and a much larger fresh intraventricular hemorrhage in the right hemisphere. e, Old pontine and cerebellar hemorrhages may be seen. f, Circle of Willis. Note the very large atheromatous plaque in the vertebral-basilar junction.

during periods of low blood pressure when the blood supply is inadequate to certain portions of the brain. On the basis of these arguments one may therefore do an intimectomy on the side in which the paralysis exists, with the hope that the total blood supply to the brain will be increased.

If there is a severe clinical disability with a partial or complete thrombosis of the internal carotid artery, this may be due either to embolism of the terminal vessels or inadequate collateral supply at the base of the brain with infarction usually in the distribution of the middle cerebral artery. Infarctions may be demonstrated at autopsy involving the internal capsule in patients

in whom the angiographic study revealed partial or complete occlusion of one or the other carotid.

Stenosis involving the carotid bifurcation may occur in conjunction with other pathologic states, and the stenosis may not be the basis for the clinical findings in the case. This fact is becoming more apparent as greater attention is given to the bifurcation area at the time that the angiogram is done. Particularly among older patients, associated stenotic lesions in the area of bifurcation or about the siphon are noted even though the primary difficulty is head injury, subdural hematoma, brain tumor, or intracranial hemorrhage. Thus, the physician should exercise care not to ascribe causative importance to a stenotic lesion of the carotid bifurcation when the disease process is to be found elsewhere. The angiograms and autopsy findings in Figure 6 are of a 66 year old male. On admission to the hospital, he had right-sided hemiplegia and total aphasia. There was a history of numbness of the left half of the body 1 year earlier. The spinal fluid was bloody. Angiograms showed bilateral stenosis of the carotid bifurcation. No mass lesion could be noted in this study, but the patient had a sudden massive intraventricular hemorrhage 10 days later and expired. Autopsy showed a large acute right parietal hematoma and smaller subacute left parietal infarct; also a healed brain stem, pontine, and cerebellar infarction, from an episode 2 years earlier. The patient was moribund from the beginning. This case illustrates the multiplicity of lesions present. Note the presence also of a large atheroma of the vertebral-basilar junction.

Atheromas may be multiple. The bifurcation, the siphon, the vertebral-basilar system, and the various large branches of the circle of Willis may show angiographically demonstrable lesions. In Figure 6, partial occlusion of the carotid bifurcation bilaterally and multiple atheromas of the basilar-vertebral system may be seen.

The prognosis in carotid artery disease depends upon the collateral blood supply, including the status of all the vessels comprising the circle of Willis—congenital variations—and possible embolization of terminal vessels. Unconsciousness and severe disability are poor prognostic signs for life and recovery. On the other hand, when a thrombosis occurs with little or no focal phenomena, or if the focal phenomena subside and improve rapidly, results may be excellent, and the patients may carry on for many years leading a relatively normal life. Therefore, if a partial occlusion is associated with focal abnormalities with rapid improvement, in such a case intimectomy may be expected to give a good result. If, on the other hand, a partial occlusion has an apoplectic onset, probably due to associated embolization and infarction, there being serious disabilities, operative intervention may not result in much improvement.

SUMMARY AND CONCLUSIONS

Our experiences with carotid artery occlusion in the neck for the period of September 1948 to May 31, 1959 are summarized. Carotid artery occlusion in the neck cannot cause a stroke unless the collateral supply of blood at the base through the carotid and the two vertebrals is deficient, or there has been a forward embolism from the atheromatous disease with implication of the small vessels of the brain resulting in varying degrees of disability, or there is a congenitally anomalous circle of Willis. In other instances in which there is an atheromatous lesion, a period of a lowered level of blood pressure may be further intensified by the presence of the stenosis, resulting in ischemia in the distribution of the vessel. This may be an important factor if one were to assume that atheromatous lesions, occurring in the secondary and tertiary branches of the main stenotic vessels, cause the blood pressure to be precipitously lower in the region of their distribution.

Early angiographic studies to detect the presence of stenosis of one or the other

carotid artery may allow repair before dangerous end results occur.

It is difficult at the present time, with the amount of information available, to say how much good is accomplished by the more normal re-establishment of blood flow through a given carotid artery by operation. Although in many instances the results may not be significant for the proximate future, they may be important for the distant future when one or the other of the vessels on the other side may be similarly involved.

Prognosis in carotid artery disease, obviously, should be very guarded. Results frequently depend upon factors other than removal of an atheroma in a given region of the vessel; the most important being the collateral supply at the base of the brain and the condition of the other three vessels in the neck.

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A CLINICAL AND AUTOPSY STUDY OF TUMOR CELLS IN THE THORACIC DUCT LYMPH

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THE FIRST DESCRIPTION of thoracic duct involvement by tumor was by Cooper in 1798. In 1848, the role of the thoracic duct in the dissemination of malignant disease was recognized by Virchow in his observation that gastric cancer was sometimes associated with enlargement of the left supraclavicular nodes. In 1880, Weigert described complete occlusion of the thoracic duct at postmortem examination by metastases from a cancer of the rectum. In 1889, Troisier reported enlarged left supraclavicular nodes from stomach and other intra-abdominal cancers. Unger stated that at the time he wrote (1896) 10 cases were on record. In his case of cancer of the uterus, there were metastatic growths in the thoracic duct, the left supraclavicular nodes, and elsewhere. In 1867, Waldeyer emphasized the retrograde spread of tumor through the intestinal lymphatics, and in 1898, Winkler pointed out the importance of the retrograde spread of tumor through the thoracic duct and its lymphatics. Schwedenberg believed that the thoracic duct was the main pathway for pulmonary metastasis of intra-abdominal cancer, though actual involvement of the duct itself was considered rare. Stevens in 1907 presented 7 cases of gastric cancer with thoracic duct and supraclavicular node involvement and pointed out that the thoracic duct plays an important role in the dissemination of intra-abdominal malignant disease by being directly involved or acting as a "simple carrier" of tumor emboli.

In 1938, Washburn reported thoracic duct invasion in 4 of 50 cases of cancer, but the cervical portions of the ducts were not examined. Viacava and Pack, in 1944, using only clinical findings reported supraclavicular metastasis in only 2.8 per cent of 4,365 cases of cancer. Willis, in 1952, reported thoracic duct involvement in 6.3 per cent of subdiaphragmatic tumors. Young, in 1955, reported thoracic duct invasion in 37 per cent of cases of carcinoma and 71 per cent of cases of lymphoma. Kausel and associates, in 1957, reported a 30 per cent incidence of metastatic involvement of the thoracic duct in 13 autopsies for malignant disease. These investigators reported nests of metastatic cells within the lumen of the duct, with no evidence of duct involvement. However, they did not believe these to be primarily embolic, but rather to be fragments of tumor broken off from a lesion already established in the duct.

METHOD

Thoracic duct cannulations are performed on patients with far-advanced carcinomas prior to administering anticancer chemotherapy. All the cannulations are performed in the operating room, utilizing 1 per cent procaine as a local anesthetic whenever possible. The technique for the isolation of the thoracic duct follows closely that described by Bierman and associates. To facilitate identification of the duct structure and the abdominal origin of the lymph the patients are given a glass of milk 30 minutes before the operation, which produces a white lymph due to the increase in chylomicrons.

The skin incision is in the left supraclavic-

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Supported in part by U. S. Public Health Service Grant C3435-C2.

TABLE I.—SOURCE OF TUMOR CELLS IN THE THORACIC DUCT LYMPH

Disease	*Patients studied**	*Tumor cells present*	*Per cent*
Carcinoma of stomach	6	3	50
Carcinoma of rectum	6	0	0
Carcinoma of lung	6	2	33
Carcinoma of breast	2	1	50
Carcinoma of ovary	2	1	50
Sarcomas	5	0	0
Colon, esophagus, Hodgkin's disease	3	0	0
Total	30	7	23

*All patients had advanced disease.

ular fossa (Fig. 1A) parallel to and approximately 2 centimeters above the clavicle, arising over the clavicular head of the sternocleidomastoid muscle, and extending laterally for at least 6 centimeters. The platysma is divided and hemostasis secured with No. 000 chromic catgut ligatures. The clavicular head of the sternocleidomastoid muscle is then identified and transected (Fig. 1B), care being taken to avoid injury to the underlying jugular vein or the anterior jugular vein in the lateral margin of the wound. When the clavicular head of the muscle is separated, the underlying cervical fascia becomes apparent with the jugular vein medially and the posterior belly of the omohyoid muscle superiorly.

The fascia is incised parallel to the lateral edge of the jugular vein (Fig. 1C), and by using blunt dissection in the *same direction* the lateral vein is cleared down to the jugulosubclavian junction. The adjacent areolar tissue is separated gently and the lymphatic duct structures will become apparent (Fig. 1D). The thoracic duct usually empties as a cistern-like structure into the subclavian vein about 0.5 centimeter lateral to the jugulosubclavian junction. However, it may empty into the jugular vein or any of its tributaries such as the transverse cervical vein. Occasionally, the latter vein or its adjacent artery may be mistaken for the duct; however, careful dissection medially will disclose the origin of the vessel, while the proximal thoracic duct will course medially and posteriorly much as a shepherd's crook going downward into the neck. Often the cervical or lateral lymphatics will be as large as the thoracic duct, approximately 0.5 centimeter, and will be identified only by further dissection of their course. After isolation of the duct with 2 No. 000 black silk ligatures the distal ligature is tied to prevent reflux venous bleeding or air embolism. The duct is incised transversely and the flow of white chyle confirms the gastrointestinal source of the lymph (Fig. 1E). Suction is usually necessary at this stage for good visualization during the insertion of a No. 18 gauge polyethelene catheter. It is difficult to insert the catheter more than 1 or 2 centimeters because of the numerous valves present in this portion of the duct. The catheter is tied in place with a No. 000 black silk ligature. The wound is closed when it is ascertained that no leakage of lymph is present. We have not approximated the cut edges of the clavicular head of the sternocleidomastoid muscle routinely, and no deformities have resulted. A light dressing is applied and the tubing put to continuous drainage. The tubing and collecting bottle are both siliconized, and heparin is added to the collecting bottle as an additional safeguard against clotting of the lymph sample. The collecting bottle is then stored in ice at the patient's bedside. The patient may be ambulatory. Continuous drainage has been maintained for as long as 12 days.

At the termination of the collection period the catheter is clamped and incorporated in the dressing. The lymph quickly clots in the tube, and the tube is then removed in 2 or 3 days. Following this technique, no fistulas have developed. If the tube is removed accidently during the drainage period the wound is reopened and the duct ligated immediately. In 1 patient so treated lymph drainage developed from the wound after ligation of the duct, the lymph arising from the bed of several supraclavicular nodes removed for biopsy pur-

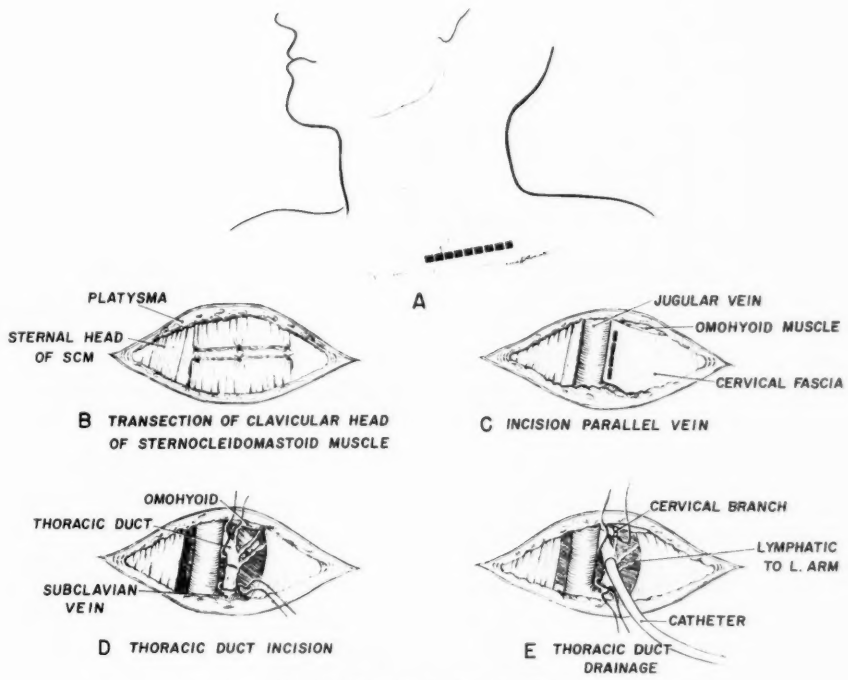


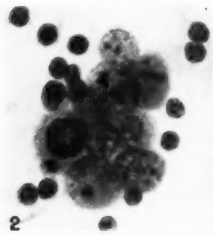
FIG. 1. Thoracic duct cannulation.

poses at the time of cannulation. The fistula closed in a period of 7 days with pressure dressings.

We have attempted clamping the heparin-filled catheter and reopening this daily for a lymph sample, after the technique of Linder and Blomstrand. After each daily lymph collection heparin is added to the catheter to prevent clotting. This intermittent collection method has the advantage of avoiding excessive lymph loss, which can reach serious proportions.

Measured aliquots of the daily lymph collection are centrifuged at 1,000 revolutions per minute for 10 minutes, and all the cellular sediment, including lymphocytes and tumor cells, is streaked on slides and stained by the Papanicolaou technique. The slides are then screened by trained technicians and reviewed by the authors. Whenever possible, tumor imprints are made for cytologic comparison.

Postmortem examination of the thoracic duct is performed at the onset of the autopsy examination. After opening the thorax in the routine manner, the right diaphragm is transected along the lateral margin, reflecting the liver and its attachments medially. The azygos vein is identified and the cisterna chyli or proximal thoracic duct is isolated between the azygos vein and the aorta. After isolating the duct in its lower portion, it is cannulated with a curved No. 19 gauge needle and 1 or 2 cubic centimeters of lymph are aspirated from the lumen. One cubic centimeter of bovine albumin is added to this lymph, which is then centrifuged at 2,000 revolutions per minute for 15 minutes, and the cellular sediment streaked on slides and stained by both the Wright-Giemsa stain and the Papanicolaou technique. These slides are then screened by trained technicians and reviewed by the authors.



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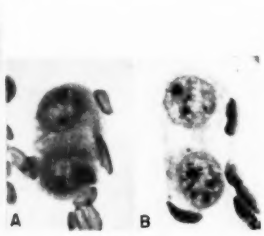

FIG. 3.

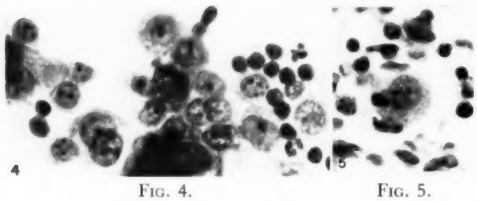

FIG. 4.

FIG. 5.

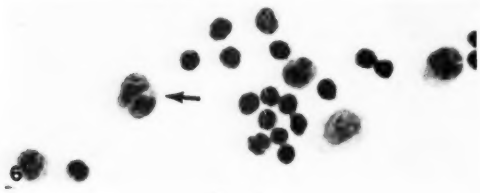

FIG. 6.

FIG. 2. Carcinoma of the stomach. Note tumor cell within clump undergoing mitosis. Papanicolaou stain, ×634.

FIG. 3. Epidermoid carcinoma of the lung. A, Tumor cells from the thoracic duct lymph. B, Tumor cells from the tumor imprint. Papanicolaou stain, ×634.

FIG. 4. Carcinoma of the breast. Papanicolaou stain, ×505.

FIG. 5. Carcinoma of the ovary. Compare size with adjacent lymphocytes and erythrocytes. Papanicolaou stain, ×505.

FIG. 6. Lymphoblasts from thoracic duct lymph. Note double nucleated cell (arrow). Papanicolaou stain, ×748.

RESULTS

To date 30 patients with far advanced carcinomas and sarcomas have been studied. Lymph flow was maintained from 1 to 12 days, the average being 6 days. The amount of lymph collected varied from a few drops to 2,500 milliliters during 24 hours or 25 milliliters per hour. Lymph flow was increased when the patient was well hydrated and taking food and fluids orally. Atropine and morphine had no effect on lymph flow. Coughing, straining, and moving about increased the flow of lymph from the thoracic duct. Sixteen of the 30 patients received anticancer chemotherapy during their cannulation period, 5 receiving actinomycin D, 4 nitrogen mustard, 2 5-fluorodeoxyuridine, and 5 THIOTEPA.

Only 1 of 20 patients gained weight during the period of duct cannulation and chemotherapy, the remaining 19 lost an average of 2.8 kilograms during the period of lymph flow. Peripheral blood counts were obtained during the same period, and no significant decrease in the peripheral white blood cell count occurred, the average being 11,350 white blood cells with 18 per cent lymphocytes at the onset, and 10,900 white blood cells with 13 per cent lymphocytes at the conclusion of the study period. Chemical analyses of the blood were made at the onset and conclusion of the period of thoracic duct drainage. At the onset the average albumin/globulin ratio was 3.73/2.11 grams per cent, and at the conclusion of lymph drainage it was 3.51/1.92 grams per cent. The average blood cholesterol levels at the onset were 48 milligrams per cent free and 158 milligrams per cent total, and at the conclusion it was 71 milligrams per cent free and 216 milligrams per cent total. The average blood prothrombin time was 67 per cent of normal at the onset and 50 per cent of normal at the conclusion. No changes developed in the serum sodium, potassium, chloride, carbon dioxide content, calcium, phosphorus, or uric acid levels when these were determined during the period of lymph flow.

The composition of the lymph was similar to but not identical with the serum. At the onset of the thoracic duct drainage the average lymph albumin/globulin ratio was 2.36/1.35 grams per cent, and at the conclusion it was 1.92/1.06 grams per cent. The average lymph cholesterol at the onset was 30 milligrams per cent free and 73 milligrams per cent total, and at the conclusion was 49 milligrams per cent free and 126 milligrams per cent total. The prothrombin time for the lymph was 20.5 per cent of normal at the onset for 1 patient and

averaged 13.7 per cent of normal at the conclusion for 3 patients.

Tumor cells were present in the thoracic duct lymph of 7 of the 30 patients. The source of these tumor cells is shown in Table I. All the patients investigated had far advanced disease with either local or widespread metastases leading to inoperability. In 6 patients with carcinoma of the stomach, 3 or 50 per cent had tumor cells in the lymph. All 3 of these patients had celiac lymph node involvement. One patient had a palliative subtotal gastrectomy and the tumor cells appeared in the lymph 1 week after the operation. Cancer cells from the lymph of a patient with cancer of the stomach are shown in Figure 2. In 6 patients with advanced carcinoma of the rectum, none had tumor cells in the thoracic duct lymph. Two of 6 patients with bronchogenic carcinoma had tumor cells in the lymph. In both of these patients the primary tumor was in the right lung; however, the mediastinal nodes were involved which may account for the passage of the tumor cells into the left thoracic duct. Cancer cells from the thoracic duct lymph of a patient with carcinoma of the lung are shown in Figure 3 and are compared to the cells obtained from a tumor imprint. Both of the patients with carcinoma of the breast had widespread disease including liver metastases, and 1 patient had tumor cells in the thoracic duct lymph, as shown in Figure 4. Both patients with carcinoma of the ovary had abdominal carcinomatosis with ascites, and 1 patient had malignant cells in the lymph of the thoracic duct, as shown in Figure 5. The 5 cases of sarcoma included: a leiomyosarcoma of the ileum with omental and liver metastases, a leiomyosarcoma of the anterior abdominal wall with pulmonary metastases, a liposarcoma of the posterior left chest wall with metastasis to the right ankle, a liposarcoma of the left hip with bilateral pulmonary metastasis, and an osteogenic sarcoma of the left femur with liver and lung metastasis. None of these patients had tumor cells in the thoracic duct lymph. The patient with carcinoma of the ascending colon had bilateral lung metastases, the patient with carcinoma of the esophagus had widespread local disease without metastasis, and the patient with Hodgkin's disease had mediastinal involvement with negative lymph nodes in the left supraclavicular fossa.

TABLE II.—TUMOR CELLS IN THORACIC DUCT LYMPH AUTOPSY STUDIES*

Disease	*Patients studied*	*Tumor cells present*	*Per cent*
Carcinoma of breast	13	3	23
Carcinoma of lung	14	3	21
Carcinoma of esophagus	3	2	67
Carcinoma of kidney, bladder	5	2	40
Carcinoma of pancreas, gallbladder	4	2	50
Melanoma, lymphosarcoma	8	3	38
Others (3 benign)	44	0	0
Total	91	15	16

*Aspiration from cisterna chyli.

Pulmonary metastases were demonstrated roentgenologically in 6 patients, none of whom had tumor cells in the thoracic duct lymph. Biopsies of left scalene nodes were positive for tumor in 5 patients, 3 of whom proved to have tumor cells in the thoracic duct lymph. Two of these patients had carcinoma of the lung, and the third had disseminated breast cancer. One patient with cancer of the stomach had tumor cells in the thoracic duct lymph, a negative left scalene node biopsy, and a positive node removed from the groin. Two other patients with cancer of the lung had metastases to the left scalene nodes without having tumor cells demonstrable in the thoracic duct lymph.

Postmortem studies were conducted on 600 patients. Due to the technical difficulty in obtaining lymph from the cisterna chyli, adequate examination was possible in only 91 patients, as shown in Table II. All of these patients expired with widespread malignant disease either associated with, or the direct cause of their demise. Tumor

cells were present in the lymph of 15 of the 91 patients, or 16 per cent. Tumor cells were present in the lymph of 3 of 13 (23 per cent) of patients with cancer of the breast, and in 3 of 14 (21 per cent) of patients with cancer of the lung. Tumor cells were also found in the lymph of the cisterna chyli from patients with carcinoma of the esophagus, carcinoma of the kidney, transitional cell carcinoma of the bladder, carcinoma of the pancreas, carcinoma of the gallbladder, malignant melanoma, and lymphosarcoma.

DISCUSSION

The amount of daily lymph flow obtained from the patients corresponded closely to that reported by Bierman who obtained flows of from 300 to 2,800 cubic centimeters per 24 hours. It seems to be a function of adequate cannulation, prevention of clotting, hydration of the patients, and the oral ingestion of food and fluids, all of which will increase the flow of lymph. Care must be taken to replace the fluid loss with water, electrolytes, and plasma if necessary to prevent hypovolemia. The duration of lymph flow is subject to such factors as lymph clotting in the tubing, accidental removal of the tube by the patient, or the clinical status of the patient. The recorded weight losses by the patients may reflect some dehydration; however, these patients were also undergoing treatment with anticancer chemotherapy, which increases anorexia and weight loss.

Of interest was the fact that with thoracic duct lymph diversion of the lymphocytes, plus anticancer chemotherapy, no marked decrease in the peripheral white blood cell count occurred in these patients. The percentage of lymphocytes in the peripheral blood also remained relatively constant. This observation does not agree with the experimental findings of Kindwall but may well represent an inadequate diversion of the lymph flow in the patients, since accessory channels develop rapidly after the cannulization. Lymphocytes may also enter the circulation via the right thoracic duct as well as these accessory channels. In the lymph obtained there were many lymphoblasts as shown in Figure 6. Bierman states that these lymphoblasts represent 5 per cent of all cells in the lymph, and he posed the question of why these lymphoblasts are so rare in the blood.

During the period of lymph flow there was some slight decrease in the serum albumin and globulin levels, but no decrease developed in the serum cholesterol levels, as might have been anticipated. No electrolyte imbalance developed; however, fluid and electrolyte replacement was carried out as needed clinically during the test period. The protein content of the lymph was lower than that of the serum, and decreased in value slightly during the test period. The values of free and total cholesterol content of the lymph was likewise less than that of the serum, and decreased slightly during the period of lymph drainage. Bierman found the cholesterol ester fraction of lymph exceeded that of blood. Linder and Blomstrand found the lymph albumin, globulin, and cholesterol fractions all less than that of the serum.

Tumor cells were identified in the thoracic duct lymph in 23 per cent of the clinical patients and in 16 per cent of the autopsy studies. This is slightly less than the incidence of duct involvement reported by Young. The frequent occurrence of tumor cells in the thoracic duct lymph and scalene node involvement is in accord with what we would expect, and may well represent a simultaneous phenomenon; i.e., node metastasis and tumor emboli passing into the circulating blood. Celis and associates emphasized the importance of thoracic duct spread of tumor emboli in the etiology of pulmonary metastasis. However, in our patients with pulmonary metastasis it was not possible to demonstrate tumor cells in the thoracic duct lymph; hence the hematogenous spread to the lung may be more important. Despite our inability to isolate the tumor cells in these cases, we believe

that passage of tumor cell emboli via the thoracic duct lymph can lead to hematogenous dissemination of the cancer, including the formation of pulmonary metastases.

SUMMARY

The technique for thoracic duct cannulation has been described as well as a method for the postmortem isolation of lymph from the cisterna chyli. Comparison of the average serum and lymph values of albumin, globulin, cholesterol, and prothrombin was presented. Tumor cells were present in the thoracic duct lymph in 23 per cent of the clinical patients and in the lymph of the cisterna chyli in 16 per cent of the autopsy cases. Patients with carcinoma of the stomach, lung, and breast appeared to have a high incidence of tumor cells in the lymph. There was a positive correlation between supraclavicular node metastasis and tumor cells in the lymph; however, no correlation was found between pulmonary metastasis and tumor emboli in the lymph. Nevertheless, we believe that the passage of tumor cell emboli via the thoracic duct into the circulating blood is an important mode of cancer dissemination.

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A FOLLOW-UP STUDY OF AORTOILIAC RECONSTRUCTION

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THE RESULTS attained in 52 patients with aortoiliac occlusion treated by reconstructive methods are presented. For the purpose of this article aortoiliac occlusion is defined as that which starts above the level of the hypogastric artery. The series includes all such patients operated upon at the Peter Bent Brigham and the West Roxbury Veterans Administration Hospitals from October 1952 to October 1958. During this period there were an additional 70 reconstructive operations for iliofemoropopliteal occlusion, the upper end of which is defined as starting below the origin of the hypogastric artery. The results in that group have already been reported (8).

Causes of occlusion. The causes of occlusion were: arteriosclerosis—chronic occlusions—in 44 cases; arteriosclerosis—acute thrombosis—in 2; arteriosclerosis and embolus in 4; and other causes—gunshot wound, graft closure—in 2 cases. Two of the arteriosclerotic occlusions were associated with thrombosed aneurysms of the abdominal aorta. Total thrombosis of the aortic lumen is an uncommon complication of such aneurysms, these 2 cases representing 5 per cent of all abdominal aortic aneurysms operated upon during the same period. The 4 patients with emboli had coexistent mitral stenosis and presented 10 days to 18 months after the embolism. They were included in the series because they also had severe aortoiliac atherosclerosis which was found and dealt with at operation. This fact undoubtedly contributed materially to the hold-up of clot at the bifurcation and its subsequent propagation.

Sites of occlusion. The sites of major vessel occlusion are shown in Figure 1. The high incidence of aortic occlusion associated with bilateral iliac occlusion and the solitary patient with isolated aortic thrombosis support the view that aortic thrombosis is usually associated with bilateral iliac disease and is in fact a secondary retrograde thrombosis. This progression of occlusion usually halted either at the origin of the inferior mesenteric or the renal arteries. Eleven patients had partial occlusions only but with symptoms sufficient to indicate surgery. Apart from the occluding lesions atherosclerosis was usually widespread in the area of the bifurcation and iliac arteries.

The incidence of additional femoropopliteal artery occlusion in 21 of the patients reflects the generalized nature of the disease. In 10 patients the blocks were bilateral. It was this group of patients, in whom symptoms were severe and disease extensive, which presented the biggest problem in selection of procedure and as to how far distally reconstruction should be carried.

Sex and age. There were 45 men and 7 women.

The ages ranged from 32 to 70 years. The mean age was 53.2 years, which is similar to that reported by DeBakey and associates for patients having surgical reconstruction for aortoiliac obstruction from arteriosclerosis. During this period there were 13 patients not included in this series who presented with such obstruction. Their higher mean age of 64 years corresponds more closely

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Aided in part by National Institute of Health Research Grant H-2036, Public Health Service.

with the nonoperative series reported by Beckwith and associates and like that series reconstruction was not performed because of severe associated vascular disease elsewhere or extensive lesions with poor "run off."

The mean age of the surgical group is also slightly lower than that for patients with iliofemoropopliteal occlusions (58.6 years, range 32 to 83 years). The reason for this is that precocious occlusion is more often seen in the aortoiliac group (Leriche syndrome) then in the femoral group.

Symptoms. The commonest symptom was intermittent claudication which occurred in 48 patients. The mean duration of symptoms was 5 years, with a range of from 9 days to 15 years. This symptom alone, if mild, was not considered a primary indication for surgery. It was usually the worsening thereof with or without rest pain which led to hospital admission. Claudication was situated at varying levels between the foot and the buttock. Buttock claudication was always indicative of iliac occlusion, although in 6 of 19 instances this occlusion was not complete. Isolated hypogastric artery occlusion in the absence of occlusion of the common iliac was not seen either at operation or on aortography. We doubt that such a situation could cause buttock claudication unless the branches of the common femoral artery supplying the buttock were also obstructed. Common iliac occlusion does not require that the patient have buttock claudication, however. One-third of the patients with occluded common iliac arteries had sufficient collateral blood supply to maintain adequate buttock circulation within the limits of their exercise tolerance.

Rest pain was associated with trophic changes varying from wasting and mild skin atrophy to severe pain, marked rubor, and general soft tissue atrophy of the foot. Early toe gangrene was seen in 3 patients. Global atrophy of the type described by Leriche was not a feature. Isolated aortoiliac disease did not thus lead to frank gangrene in any of our patients. This observation contrasts

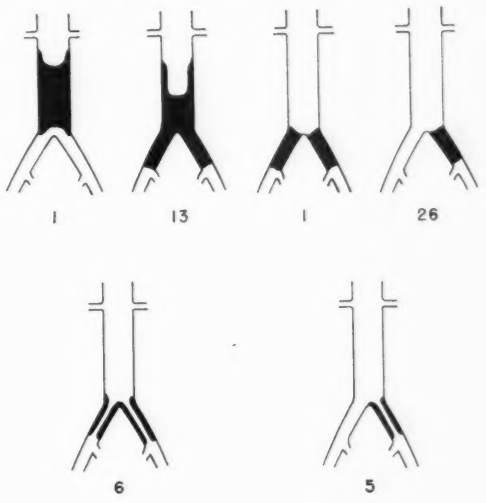

FIG. 1. Site of major occlusion in 52 patients. Only those lesions dealt with surgically are depicted. Most of the patients demonstrated additional arteriosclerosis contiguous to the areas shown.

with the finding in the iliofemoropopliteal group in whom gangrene occurred in 17 of 84 cases. The comparative excellence of the collateral circulation around disease at the aortic level is possibly sufficient to maintain adequate resting blood flow in the absence of a more peripheral occlusion.

Of the 16 patients with more severe ischemia 10 had occlusions of the femoral artery below the higher lesion, and 2 had recent acute occlusions in which collateral circulation had not yet developed. If the common femoral artery were occluded, blocking the orifice of the deep femoral, severe ischemia was always present.

Impotence was recorded in only 8 of the 45 males, and as 4 of these had a unilateral iliac occlusion the value of the symptom in indicating a bifurcation block was doubtful.

Associated disease. Twenty-five patients had associated vascular disease, 21 were hypertensive with a blood pressure greater than 150/100 millimeters of mercury, and there were 13 with evidence of vascular disease

TABLE I.—TYPES OF OPERATION—IMMEDIATE RESULTS

	Total	Deaths	Hospital closure	Discharged patent	
				No.	Per cent
Thrombendarterectomy...	19	1	2	16	84
Grafting with or without thrombendarterectomy...	33	7	2	24	73
Total: No.	52	8	4	40	
Per cent		15.4	7.7		76.9

in the heart, brain, or kidney. These conditions do not, we believe, constitute a contraindication to surgery provided the patient can utilize the improvement in circulation obtained in terms of adequate function of other systems. The mortality and complication rates were not higher in this group.

Diabetes occurred in only 1 patient suggesting that this condition plays no special part in the etiology of occlusion of the more central vessels.

Aortography. Aortography was employed in all but 1 patient. The lower arterial tree was often not adequately visualized, and femoral arteriography was then performed either preoperatively or at operation to establish the state of the distal arteries. This is of considerable importance not only in determining the possibility of reconstruction but in deciding the distal point to which it should be carried. For the lower anastomosis adequate length of patent popliteal artery with minimal disease and a good "run off" is to be preferred to a ragged femoral artery which may be occluded in midthigh.

Operation. Fifty-two operations were performed. Table I shows the operations classified according to type and the results thereof. The method of treatment was adapted to the site of the occlusion in each patient and was thrombendarterectomy, grafting, or a combination of these.

Thrombendarterectomy alone was performed on the more localized high occlusions, particularly when there was no lower occlusion requiring treatment, and therefore in the more favorable cases. The technique was one of longitudinal arteriotomy. In the aorta this was usually carried to a point about half way between the aortic bifurcation and the renal artery. Removal of more proximal thrombus was accomplished by using digital compression of the upper abdominal aorta for hemostasis (Fig. 2). In the iliac arteries this technique was used, or if the occlusion was extensive, multiple incisions were made and intraluminal stripping was performed.

Grafts were frozen, irradiated, and stored homografts except for 3 synthetic grafts, namely, 2 of woven dacron and 1 ivalon sponge tube. End-to-side anastomoses were used where possible, but exceptions were made when the vessel to which the anastomosis was being done had been transected for other reasons. In 1 patient the graft was anastomosed to the splenic artery at the upper end rather than directly to the aorta or iliac artery. Grafting was carried out below the inguinal ligament in 19 patients, in 12 of these as a bypass to the popliteal artery. The grafting procedure was combined with a local thrombendarterectomy in half the cases, it being used in those in which it was necessary to obtain arterial wall suitable for suture or to prevent the formation of "flap valves" of a frayed plaque at the lower anastomosis.

RESULTS

Mortality. There were 8 deaths (15.4 per cent) in 52 operations. The major causes were: ischemic nephrosis in 2 cases; rethrombosis in 2; myocardial infarct in 1; innominate artery thrombosis in 1; secondary hemorrhage in 1; and ileus and bronchopneumonia in 1. Two of the deaths were in patients with acute thrombosis, both seriously ill, in whom there was little prospect of success. It was thought, however, that the alternative would be death due to progression of thrombosis and gangrene of both lower extremities. Two deaths from arterial thrombosis elsewhere followed secondary operation for local thrombosis at the site of reconstruction. Two major rethromboses which led to renal failure and gangrene are

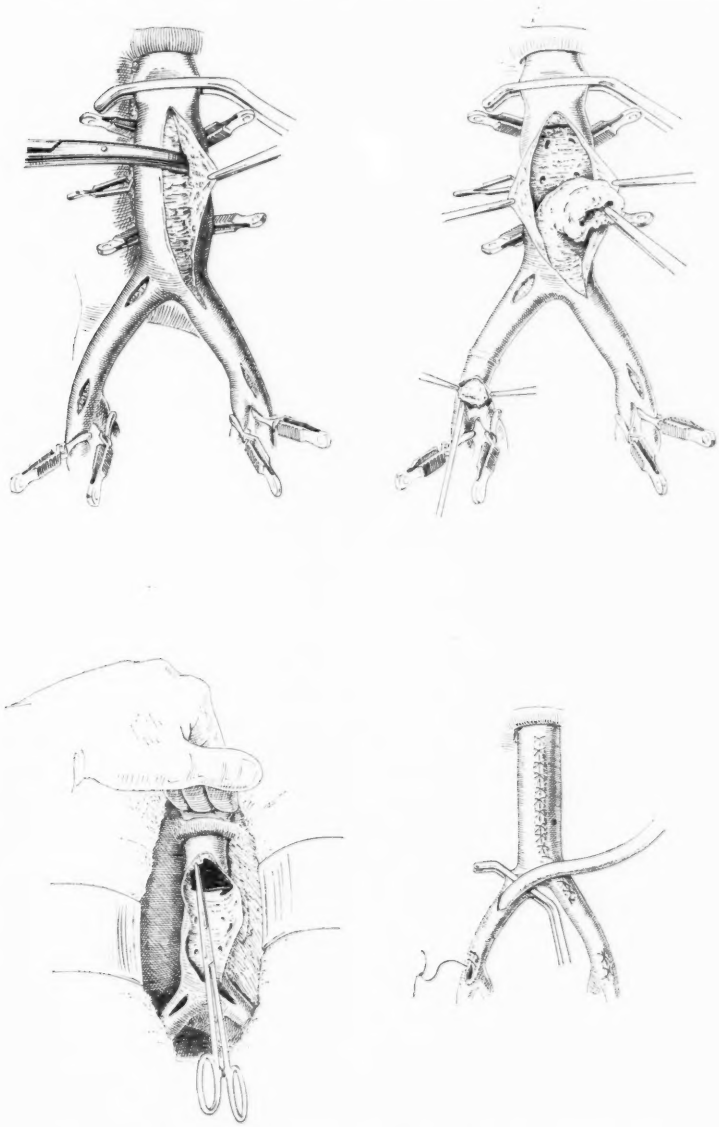

FIG. 2. Technique of thrombendarterectomy of aorta and common iliacs.

unexplained. Both of the patients had been left with bilateral occlusive arterial disease remaining below the reconstructed level. Femoral artery hypotension at the time of surgery and postoperative hypotension could have accounted for the rethromboses which occurred within 24 hours of operation.

Postoperative complications. Closure of the reconstruction occurred in the early postoperative period in 5 patients other than those who died. One was successfully reoperated upon. The 4 others returned to their preoperative state; in 2 of the 4, gangrene occurred as it had been destined to do with-

TABLE II.—LATE CLOSURES IN RELATION TO TYPE OF OPERATION

	Total	*Hospital deaths and closures*	*Available to follow-up*	*Late closure*	*Patent*	
					Patients	*Per cent available to follow-up*
Thrombendarterectomy	14	3	11	2	9	82
Grafting with or without thromb-endarterectomy	26	6	20	9	11	55
Total	40	9	31	11	20	64.5

40 patients available to follow-up longer than 1 year.

out reconstruction. These 2 had additional femoral occlusions. In 2 others secondary hemorrhage developed from homografts.

Complications not involving the reconstructed segment numbered 12. Ileus was the commonest, as a result of the prolonged intra-abdominal exposure and stretching of the mesenteries. The others followed the pattern of complications after any major surgery.

Early results. In 40, or 77 per cent, of the 52 patients operated upon, the reconstructions were patent at the time of discharge from the hospital. This figure represents 90 per cent of the 44 discharged alive. Patency was judged by the presence of normal pulses below the reconstruction. The more favorable results with regard to mortality and patency in thrombendarterectomy alone are the result of selection of short high occlusions for this procedure. Although very successful in localized femoral occlusions in the absence of aortoiliac disease as previously reported (8), it was never done in the present group below the inguinal ligament. Bypass grafting was the procedure employed beyond that point. The choice was made because of the shorter time and incision required for the bypass procedure in a patient with a long lower block in whom upper reconstruction was necessarily a major procedure.

Twenty-eight of the patients with patent reconstructions had no symptoms of vascular insufficiency on early follow-up. The 12 others had symptoms ranging from minimal claudication in 5 to an unimproved state in 2, these patients all having evidence of disease in the femoral artery or below not treated at the primary operation.

Late results. The late results are considered in the 40 patients operated upon before October 1957 and observed for a period of 15 months or greater. Excluding deaths, hospital closures, and 1 patient lost to follow-up, there are 31 remaining patients. The varying duration of follow-up is seen in Figure 3, the average being 2 years and 9 months. The occurrence of closure was judged by recurrence of symptoms, loss of pulses, and in a few was confirmed by arteriography. Six of the 11 closures occurred within the first year but there was no predictability of the time of the other closures (Fig. 4), and there seems to be no reason to suppose that more will not occur in the future. The higher incidence of closure in the first year reported elsewhere as well as that apparent in this series may be partly due to inadequate duration of follow-up, only 9 of our whole series having been observed more than 4 years.

Grafts were involved in most closures, but again this may be a reflection of the relative severity of the disease in this group (Table II). The effect of closure was usually a return to preoperative objective status though some patients had a residual subjective improvement. In only 1 did the reocclusion lead to gangrene and amputation. Two were reoperated upon, 1 successfully. The site of closure in this group was in the reconstructed segment and did not spread to involve vessels patent at the original operation. It seems, therefore, that reocclusion depends on processes within the area of reconstruction and not on continuing disease above or below. Four of this series have died of dissociated disease since discharge, 3 with probable myocardial infarction and 1 of

malignant carcinoid. In addition to closure the single late complication of note has been 4 aneurysms occurring in homografts. Of these, 2 remain small and asymptomatic, 2 have ruptured and have been repaired.

Aortopopliteal or iliopopliteal grafts. In 10 of the 21 patients who had coincident femoropopliteal occlusions, only the aortoiliac element of the disease was treated. In only 3 of them was symptomatic improvement noted and 2 of the 3 suffered later closures of the reconstructed segment.

In the remaining 11 patients grafts were inserted between the aorta or the iliac artery above and the popliteal below. All the 9 survivors but 1, who had an associated posterior tibial block, became asymptomatic. One whose reconstruction closed after 21 months was reoperated upon successfully with a similar graft, and in 6 or 55 per cent the grafts have now remained open for more than 1 year (mean 19 months).

DISCUSSION

Although many series of aortoiliac reconstructions for obliterative disease have been reported with "success rates" of over 90 per cent, relatively few have been followed up for a long period of time. Butcher and Robinson reporting 26 bifurcation grafts, 19 of which were done for occlusive disease, found 15 grafts patent at 12 to 35 months postoperatively. Cockett and Norman reported 8 out of 15 cases fully successful at over a year, and they noticed an incidence of late closure of from 10 to 30 per cent. Our series confirms these findings. The factors influencing late closure are not at present fully understood. The fact that the process occurs usually only within a reconstructed segment is against the disease progression in the parent artery being an important factor. Szilyagyi suggests that the grafts act as antigens and that graft closure may be a rejection phenomenon which is greater in the femoral grafts because the proportion of muscular tissue to elastic tissue in the arterial wall is there increased. This, however, can hardly be a factor in thrombendarterectomy.

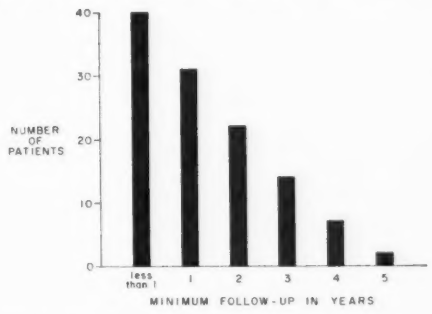

FIG. 3. Duration of follow-up in 40 patients discharged with open reconstructions. Intervals in years since operation are plotted against the numbers of patients fitting into each interval category.

Some of the material procured from our patients at autopsy or reoperation allowed us to study the reconstructed segment at later dates. This was reported upon in a previous paper (8). In that study atheromatosis was observed in the reconstructed segments after several months, but it was minimal in degree except in 2 cases in which it was fulminating and presumably due to graft rejection. It was believed that delayed graft reaction and slow mural thrombosis were the principal causes of closure.

The success rate of 65 per cent in those discharged with patent grafts and followed up for more than 1 year contrasts favorably with our series with femoral reconstructions in which the rate was 31 per cent. The most likely reason is the larger size of the vessels and the increased velocity of flow in the upper arteries. Of the 12 patients with closures both in hospital and after discharge

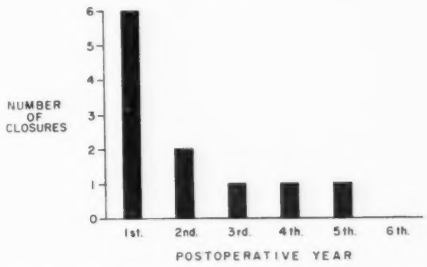

FIG. 4. The interval from operation to closure in 11 late closures is expressed in terms of the postoperative year in which the closure occurred.

who did not have long reconstructions, only 4 (33 per cent) had no evidence of occlusive disease in the femoral artery. The importance of a rapid flow in the reconstructed segment is thus supported. This may be particularly important during the period of formation of endothelium which has been shown by Poole to be very slow in animal arteries denuded of their endothelial lining.

The fact that, in patients with simultaneous aortoiliac and femoropopliteal occlusions, relief was experienced by only 3 of 10 in whom merely the upper obstruction had been dealt with as contrasted with 8 of the 11 in whom additional long bypass grafts to the popliteal artery had been used argues strongly for the more extensive operation. The upper operation alone may be recommended, however, when the lower block is not reconstructible, such as when the popliteal artery bifurcation is blocked, since some benefit may ensue. If a patient requires bilateral long grafts it has been our practice to reconstruct the aortoiliac segment and do the bypass graft to one popliteal artery, leaving the other side for a second operation. This is done because of the undue length of the bilateral procedure.

It is emphasized that this type of series differs from that of Beckwith and associates who surveyed 49 patients not operated upon and followed up for from 1 to 6 years. The age group of the seventh decade contained more cases than any other decade in their series, whereas in ours the age group of the sixth decade preponderated. Twenty-two of their 49 patients died in the 6 year period, whereas only 4 of our 40 patients died. This observation is mentioned only to emphasize that different series differ greatly in the clinical material contained therein.

It is our belief that the results in this group have been good enough to recommend operation on all symptomatic patients as soon as the diagnosis is made. This is an approach which is more radical than that used in patients with iliofemoropopliteal occlusion alone since the late patency rate in that group is only half that of the operations for more proximal disease, and the incidence of postclosure gangrene higher.

SUMMARY

1. The results of surgical reconstruction for aortoiliac obliterative arteriosclerosis in 52 patients are reported.

2. Operative mortality was 15.4 per cent.

3. The late closure rate for patients leaving the hospital with patent segments and being followed up for at least 1 year was 35.5 per cent, most closures taking place in the first year. In only 1 patient with late closure did gangrene occur.

4. In patients with both aortoiliac and femoropopliteal obstruction relief of symptoms was obtained in only 3 of 10 patients in whom the upper block alone was dealt with as contrasted with 8 of 11 in whom both the upper and lower blocks were reconstructed at once.

5. A more radical approach to reconstruction is recommended for arteriosclerosis obliterans involving the aortoiliac segment than for that involving the femoral segment alone.

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THE ESTIMATION OF HEPATIC BLOOD FLOW USING INDOCYANINE GREEN

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THE MEASUREMENT of blood flow through the liver remains a challenging problem. In 1945 Bradley and associates reported the first clinically applicable method of estimating hepatic blood flow. This method, which utilizes the extraction of bromsulphalein by the liver, involves constant infusion of dye and hepatic vein catheterization for sampling. Other methods of estimating hepatic blood flow are based upon the clearance of certain substances, such as chromic phosphate and colloidal gold, which are extracted selectively, although not exclusively, by the liver. Still another method, recently described by Reichman and associates, utilizes the Stewart-Hamilton indicator-dilution principle.

The introduction of indocyanine green, initially used by Fox and associates in cardiovascular studies, offers a new approach in the study of hepatic blood flow. This dye has the advantage that it is extracted from the blood exclusively by the liver and passes via the bile into the intestinal tract.

The present study was undertaken to evaluate the disappearance rates and extraction ratios of indocyanine green in control and cirrhotic patients, and to estimate hepatic blood flow on the basis of these data.

MATERIAL AND METHODS

Studies were performed on 36 subjects: 30 controls and 6 patients with cirrhosis. In 10 controls and in all 6 cirrhotic subjects, hepatic vein catheterization was performed and extraction ratios as well as disappearance rates were obtained. In 20 additional controls disappearance rates were measured. In 6 controls and 5 cirrhotic patients extraction ratios and disappearance rates were obtained both after a single injection and with a constant infusion of dye.

Indocyanine green (0.15 mgm. per kgm.) was injected into an antecubital vein, and peripheral blood samples were withdrawn from the femoral artery or vein. Hepatic venous samples were withdrawn through a catheter placed under fluoroscopic control into the right hepatic wedge. Samples were withdrawn at 1 minute intervals for 5 minutes, 2 minute intervals to 11 minutes, and 5 minute intervals to 26 minutes after dye injection. For determinations using the Fick principle with constant infusion, a priming dose of 1.2 milligrams of indocyanine green per liter of blood volume was followed by an infusion of 1.0 to 1.4 milligrams per minute. These dosages were reduced in the cirrhotic patients. After 15 minutes of constant infusion, samples were withdrawn from the hepatic vein and peripheral vessel at 2 minute intervals.

Each blood sample (2.5 ml.) was placed in an oxalated tube and centrifuged for 30 minutes at 1,200 revolutions per minute. From each sample, 1.0 milliliter of plasma was pipetted, diluted to 3 milliliters with saline, and recentrifuged for 30 minutes. The specimens were then analyzed for indocyanine green on a Beckman DU spectrophotometer at 810 millimicrons.

CALCULATIONS

In the constant infusion experiments utilizing the Fick principle, hepatic blood

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Supported in part by funds from Grants HTS 5170 and H-2826 National Heart Institute, National Institutes of Health, U. S. Public Health Service.

TABLE I.—DISAPPEARANCE RATE CONSTANTS (k) AND EXTRACTION RATIOS IN 30 CONTROLS

Case	Disappearance rate constant (k)	Extraction ratio
1	.154	.85
2	.171	.89
3	.219	.92
4	.171	.85
5	.368	.89
6	.368	.82
7	.281	.88
8	.242	.84
9	.189	.98
10	.171	.88
11	.159	
12	.171	
13	.174	
14	.177	
15	.368	
16	.192	
17	.225	
18	.279	
19	.225	
20	.225	
21	.263	
22	.248	
23	.219	
24	.211	
25	.236	
26	.215	
27	.384	
28	.181	
29	.230	
30	.242	
Mean	.232	.88
S. D.	.065	.043
S. E.	.012	.014

TABLE II.—DISAPPEARANCE RATE CONSTANTS (k) AND EXTRACTION RATIOS IN 6 PATIENTS WITH CIRRHOSIS

Patient	Disappearance rate constant (k)	Extraction ratio
J. P.	.029	.29
N. W.	.112	.53
W. P.	.075	.37
J. L.	.144	.60
S. R.	.018	.09
F. S.	.184	.57

flow was calculated from the formula

$$\text{H.B.F.} = \frac{\text{mgm. dye infused per minute}}{C_{PV} - C_{HV}} \times \frac{1}{1\text{-Hct.}}$$

where C_{PV} equals concentration of dye in a peripheral vessel and C_{HV} equals concentration of dye in the hepatic vein. Peripheral concentrations of dye remained sufficiently constant that no corrective factor ($\triangle P$) was necessary.

In the single injection technique, hepatic blood flow was calculated from the formula.

$$\text{H.B.F.} = \frac{k \times \text{blood volume}}{\text{extraction ratio}}$$

TABLE III.—COMPARISON OF HEPATIC BLOOD FLOW DETERMINED BY CONSTANT INFUSION AND SINGLE INJECTION METHODS (MILLILITERS PER MINUTE)

Patient	Age	Sex	Weight, kgm.	Type	Constant infusion	Single injection
J. S.	14	F	40	Contro	1100	1100
W. L.	26	M	72	Control	2400	2800
E. R.	36	M	89	Control	2200	2200
D. H.	42	M	61.3	Control	1800	1200
J. D.	50	M	70	Control	1700	1300
J. P.	68	M	45.5	Cirrhosis	400	500
N. W.	36	M	60	Cirrhosis	1400	1300
T. K.	56	M	65.9	Control	1000	1000
W. P.	37	M	104.5	Cirrhosis	1800	2000
F. S.	51	M	67.7	Cirrhosis	2000	1600
J. L.	41	F	50.9	Cirrhosis	900	900

TABLE IV.—EXTRACTION RATIOS AND DISAPPEARANCE RATE CONSTANTS: COMPARISON OF SINGLE INJECTION AND CONSTANT INFUSION METHODS

	Disappearance rate constant		Extraction ratio	
Patient	Single injection	After constant infusion	Single injection	During constant infusion
J. D.	.189	.120	.98	.77
T. K.	.170	.100	.88	.84
W. L.	.36		.82	.78
E. R.	.28		.88	.79
D. H.	.24		.84	.72
J. P.	.029	.024	.29	.24
N. W.	.112	.085	.53	.65
W. P.	.075	.084	.37	.35
F. S.	.184	.135	.57	.59
J. L.	.144	.113	.60	.44
S. P.	.018	.013	.09	.07

where k is the disappearance rate constant, derived according to Dobson and Jones.

Blood volumes were estimated by extrapolating the disappearance slope to the initial concentration.

RESULTS

In 30 control patients the mean disappearance slope was .232 with a standard deviation of .065 and a standard error of .012 (Table I). In 10 controls the mean dye extraction ratio was .88, with a standard deviation of .043 and a standard error of .014 (Table I). Within a wide range of values for the disappearance rate constant (1.5 to .36) the extraction ratio remained relatively constant.

Among the 6 cirrhotic patients a wide range of disappearance rate constants and extraction ratios was observed (Table II). The comparison of these determinations in

controls and cirrhotic patients showed little overlap (Figs. 1, 2, and 3).

In 11 patients (6 controls and 5 cirrhotic subjects) hepatic blood flow was calculated by using both the single injection technique and the constant infusion method. Close correlation between the values obtained by these two methods was observed (Table III).

The disappearance rate following cessation of a constant infusion of dye was decreased as compared with that following a single injection (Table IV). Similarly, extraction ratios during constant infusion were usually lower than values obtained after single injections (Table IV).

DISCUSSION

The validity of indocyanine extraction in the measurement of hepatic blood flow is dependent upon the assumptions that the dye is removed from the blood exclusively by the liver and that the hepatic venous sample is representative of the entire hepatic venous outflow. Wheeler and associates demonstrated that essentially all the dye administered intravenously in the dog was recovered in the bile and that the dye was not reabsorbed from the intestinal tract. Differences in indocyanine green extraction between the right and left hepatic lobes have not been evaluated, although reports of such studies using other indicators suggest that the error thereby introduced is not great.

In the control patients evaluated in this study, the extraction ratio of indocyanine green remained relatively constant within a rather wide range of values for the disappearance rate constant. These findings suggest that, in normals, an extraction ratio of 0.88 may be assumed, and by using this corrective factor hepatic blood flow may be estimated from the disappearance rate. If such a method proves valid it would obviate the need for hepatic vein catheterization and allow calculation of hepatic blood flow from peripheral blood samples after a single injection of dye.

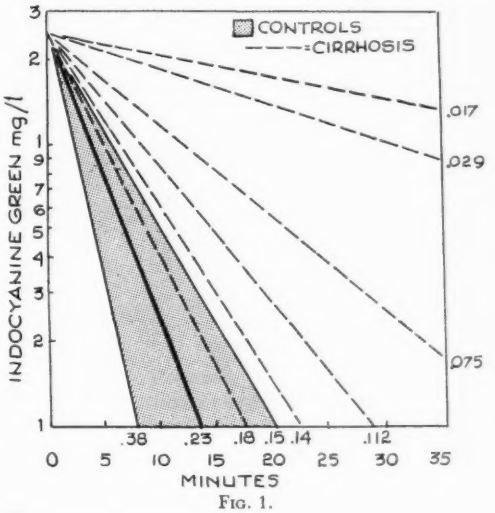

FIG. 1.

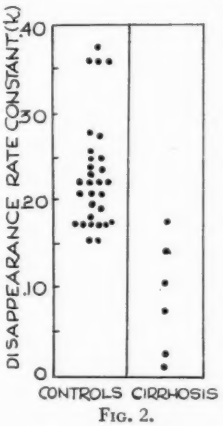

FIG. 2.

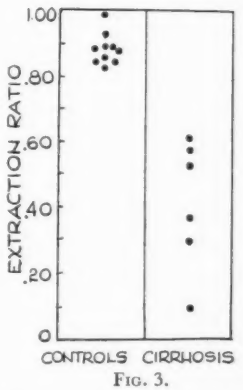

FIG. 3.

FIG. 1. The range of disappearance rate constants in control patients is represented by the shaded area, and the heavy line in the shaded area indicates the mean. The broken lines represent disappearance rate constants in 6 cirrhotic subjects.

FIG. 2. Values for the disappearance rate constants among 30 control patients and 6 cirrhotic patients.

FIG. 3. Values for the extraction ratios among 10 control patients and 6 cirrhotic patients.

Among the 6 cirrhotic subjects studied, a wide range of values was observed in both disappearance rates and extraction ratios. In comparison of cirrhotic patients with controls, there was slight overlap in disappearance rates but no overlap in extraction ratios (Figs. 2 and 3). No normal patient had a disappearance rate constant below .154,

although this value is only 1.35 standard deviation units below the mean. All patients with cirrhosis showed extraction ratios more than 3 standard deviation units below the mean. Although the number of patients with cirrhosis in this group is small, perhaps additional studies may demonstrate a definite relationship between disappearance rate and extraction ratio.

The single-injection technique of measuring hepatic blood flow was compared with the constant infusion method in 11 patients, 6 controls and 5 cirrhotics. There was close correlation between the values obtained by the two methods, both in controls and cirrhotic patients. Although hepatic vein catheterization was used in this group, the single injection technique avoided the difficulties associated with maintaining constant peripheral blood levels, a problem especially apparent in subjects with cirrhosis when the bromsulphalein method is used.

The depression of extraction and clearance after infusion of dye may represent saturation of the dye-excreting mechanism. It has been suggested by Wheeler and associates that the dye is rapidly stored in the liver and then slowly secreted into the biliary tract.

The low disappearance rate seen in cirrhotic subjects compared with controls (Fig. 2) suggests that a simplified modification of this test might prove of value as a liver function test in the rapid evaluation of patients with suspected cirrhosis, a rather common problem in cases of upper gastrointestinal hemorrhage.

SUMMARY

1. Studies with indocyanine green, a dye extracted exclusively by the liver and excreted in the bile, have been performed in 30 control patients and 6 patients with cirrhosis.

2. In control patients the extraction ratio of dye remained relatively constant through a wide range of disappearance rates, suggesting that hepatic blood flow may be estimated from peripheral venous samples in this group.

3. Among the 6 patients with cirrhosis there was a wide variation of disappearance rates and extraction ratios, although there was practically no overlap with the values in the control group.

4. Hepatic blood flow was determined in 11 patients by both the single injection technique and the constant infusion method. There was close correlation of the values obtained by the two methods, both in controls and in cirrhotic patients.

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EDITORIALS

PORTAL VEIN OBSTRUCTION—CAUSE OF, OR CURE FOR PORTAL HYPERTENSION

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IN THE JULY 1959 ISSUE of SURGERY, GYNECOLOGY & OBSTETRICS, Large and Johnston have discussed the problem of portacaval shunt operations and have indicated their strong preference for the incomplete or side-to-side variety over the complete or end-to-side. They base this choice mainly on their conviction that it is harmful to divert the portal blood entirely away from the liver and that the decompression of the portal system accomplished by their technique is superior to other incomplete shunts (e.g., splenorenal) and at least equal to the more commonly utilized end-to-side portal vein to vena cava procedures. A measure of superiority to the latter is also suggested in the treatment of ascites due to cirrhosis by virtue of the side-to-side procedure's potential for draining venous blood from the liver as well as the visceral portal bed. These thoughts on the problem are not presented as new but are evidence of increasing attention being paid to this type of procedure. But before other surgeons to whom the authors' pleas are directed are persuaded to adopt this procedure, they might also consider that those who still prefer the end-to-side method might do so on grounds other than those presented.

In the first place, while there is definite evidence that diversion of all of the portal blood from the liver may be harmful or at least undesirable in a normal animal, the evidence that the same is true in the presence of cirrhosis or of portal hypertension without cirrhosis is much less convincing. Certainly many complete shunts have been accomplished in cirrhotic patients without the harmful effects cited, and even when untoward results follow this type of procedure it is by no means established that diversion of the portal stream is the only or even the main culprit.

But more important considerations make it unnecessary to prolong the argument on this point. It can be accepted that it is undesirable to divert the portal blood from its natural course unless some positive good is thereby obtained. This leads to a consideration of the most important question of all—what is the mechanical nature of the lesion being treated? What is the cause of portal hypertension?

In the absence of any discussion of this question in the subject article, it can only be assumed that Large and Johnston consider that the lesion being treated is a mechanical obstruction to the flow of portal vein blood through the liver. It is not surprising that they so consider, since this is the classical explanation for this clinically important condition—increased resistance, portal obstruction, portal bed block are terms universally used to describe it, and thrombosis, scarring, cellular edema, distortion of the vascular channels by irregular

regeneration of liver tissue are pathologic lesions assumed to be the cause of the mechanical lesion. If mechanical obstruction is the defect to be treated, then the incomplete shunt may be preferable to the complete one, but if it is not, the incomplete shunt may be not only less desirable but actually potentially harmful. And so it is necessary to examine this fundamental issue.

Is mechanical obstruction the cause of clinical portal hypertension? Does mechanical obstruction exist in clinical portal hypertension? Lesions capable of causing such obstruction have been found in many patients with portal hypertension—thromboses, tumors, cysts, kinks, and, most often reported, cirrhosis of the liver. But when the lesion is reported to be present it is almost never accompanied by evidence that it actually caused obstruction. In many cases of portal hypertension no actual mechanically obstructing lesion can be demonstrated.

Does cirrhosis cause obstruction to the flow of portal blood? McIndoe's experiments are often quoted as showing that it does, but Herrick's and Dock's perfusion studies are equally convincing that even advanced cirrhosis may not be accompanied by effective increased resistance. It is surprising that little else can be found in the medical literature to demonstrate this point.

Can clinical portal hypertension be reproduced by obstructing the portal vein? The answer is unqualifiedly no—and this fact is amply substantiated by numerous reports. A temporary rise in pressure can readily be demonstrated by applying an obstruction, but this is soon followed by opening of collateral pathways and a return to normal pressures. The splenomegaly, varices, and congestion of clinical portal hypertension do not ensue. It would seem to be adequately established that in the portal vein of man, as well as in experimental animals, obstruction causes diversion of flow at normal pressures, just as it does in any other vein where collateral circulation is available.

So it seems that evidence presently available would warrant the following conclusions: (1) In clinical cases of portal hypertension a lesion capable of producing mechanical obstruction to the flow of portal blood is often not demonstrable, and if one is present it is seldom if ever established that it is more than coincidental or that it is not the result rather than the cause of the portal hypertension. (2) Portal hypertension cannot be reproduced in its clinical form by obstructing the portal vein experimentally.

A form or degree of portal hypertension resembling that seen clinically can be created by obstructing the outflow tract of the liver. The difference might well be the factor of the contribution to hepatic blood flow via the hepatic artery. This theory suggests further consideration of the only other factor which has been discussed as possibly causing clinical portal hypertension, that of intrahepatic arteriovenous shunting. Herrick's experiments were among the first to propose this possibility, and bits of evidence are continually showing up to suggest that this factor may be important. For example, dyes or radioactive substances injected into the hepatic artery have been found to reflux into the portal vein from the liver. Certainly the congestion and persistent venous hypertension which continue and increase in spite of the formation of tremendous collateral circulation more nearly resemble an arteriovenous shunt mechanism than they do the situation created by the application of a mechanical block to the portal vein. The point to be remembered is that if arteriovenous shunting is the cause of portal hypertension rather than simple mechanical obstruction, the incomplete portacaval shunt is not only inferior to the complete one but is actually contraindicated, since it would increase the "leak" from the hepatic artery. Furthermore, the only valuable part of the complete shunt would be the interruption of the portal vein; in other words, if the lesion being treated is an arteriovenous shunt and not simple mechanical obstruction, interruption of the main portal vein should give the same results as the more complicated

anastomotic procedures. It is surprising that for all the investigations that have been carried out on the problem of portal hypertension, there is nowhere to be found one which demonstrates what results could be expected of ligation of the portal vein in well established cirrhosis with portal hypertension.

The selection of the preferable surgical procedure for treating portal hypertension must rest, therefore, on a better knowledge of the physiologic lesion which causes the trouble rather than on the technical ease of the procedure, as suggested by Large and Johnston. And better knowledge of the lesion will probably involve a more precise determination of the relative role of arteriovenous shunting. It could be suggested that hepatic artery angiograms might give more information than injections of dyes or radioactive materials. Studies of portal vein and hepatic artery circulation with the sensitive and accurate flowmeters recently described should yield much greater and more reliable information than previously available by indirect measurements of total hepatic blood flow or by attempting to interpret direction and volume of blood flow from isolated readings of venous pressures. And surely someone with proper clinical and experimental facilities available should be curious as to what would occur to the hemodynamics of the portal system afflicted with portal hypertension if the portal vein were simply ligated and not anastomosed to anything. The knowledge that the temporary hypertension created in the normal portal bed by this procedure soon returns to normal must make one wonder why it should not do so in the cirrhotic unless there is still another lesion elsewhere in the portal bed.

A plea might therefore be directed to investigators interested in this subject to consider more critical examination of this simple yet fundamental problem—the true cause of portal hypertension. Mechanical obstruction, universally considered to be the answer, occasionally but too infrequently challenged, fails to satisfy a critical analysis, finds favor only in its potential for causing temporary increase in pressure and because of the frequent association of portal hypertension with lesions capable of causing obstruction. The actual cause and effect relationship is never adequately demonstrated, and application of the suspected cause does not reproduce the expected effect.

Arteriovenous shunting, on the other hand, could offer a better explanation of many of the phenomena seen. At least, it is a sufficiently attractive possibility to require that it be adequately proved not to be a factor before proper selection of the best surgical procedure for the treatment of clinical portal hypertension can be made. If simple ligation of the portal vein should be found to be as effective in reducing portal hypertension as the more complicated surgically constructed shunts, the argument over the preferable type of shunt would cease to exist, and a significant advance in the treatment of an important and distressing clinical problem would be made.

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THE SIGNIFICANCE OF CANCER CELLS IN THE BLOOD

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THE FREQUENCY with which cancer cells may be found in the blood of patients with malignant disease has received much attention, but the significance of such cells in terms of prognosis and suitable therapy for these patients has not been determined. Although considerable speculation has resulted, most of it has been based on unproved, preconceived ideas, or suggested by extrapolation of data from studies of transplantable animal tumors. Recently, Engell concluded that the presence of tumor cells in the blood has no prognostic import.

The first question of major importance concerns the viability of the exfoliated cells and their ability to overcome the patient's defenses and to form metastases. The fact that blood-borne metastases do occur demonstrates unequivocally that some of these cells are viable and capable of producing metastatic growth. It is necessary only to recall one patient having a very large primary tumor without evidence of metastatic growth, and another patient having malignant melanoma or breast cancer with literally thousands of metastases, in order to realize how great the variations must be in the conditions permitting tumor cells to survive.

Laboratory proof of the viability of cancer cells isolated from the blood is not easy to obtain. Supravital stains and metabolic studies indicate that certain enzymatic systems remain active, but little information is gained concerning the biologic properties of the cell in terms of its growth potential. Assay of viability by inoculation of small numbers of human cancer cells into tissue cultures, egg embryos, conditioned laboratory animals, the anterior chamber of the guinea pig eye, and other special sites is successful in very few instances.

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Tissue culture is a promising method for the growth of both normal and malignant cells. Better culture methods are being developed; for example, Puck and Marcus reported that irradiated cells will support the growth of single human cells of some culture lines. Unfortunately, the diagnosis of cultured cells depends ultimately on morphologic criteria which are nonspecific, and many such cells undergo "spontaneous" transformations in various media. The fact that every tumor is made up of a whole spectrum of cells with differing characteristics—even differing chromosome numbers—makes absolute identification difficult. The extent of this problem is demonstrated by reports of the growth of epithelial cells with some malignant characteristics from normal blood and bone marrow.

Taylor and Vellios describe their failure to grow tumor cells from the blood by implantation of the buffy coat containing such cells back into the donor patient. This method is acceptable only when patients with malignant disease volunteer for such studies and might derive some personal benefit from them. Furthermore, it has been found by Grace and Kondo that autologous implantations of tumor fragments and cell suspensions, even in patients with advanced disease, result in a low incidence of "takes." These preliminary studies indicate that a maximum of 5 to 8 per cent of autologous tumor cell suspensions will survive.

Under the circumstances, the survival and growth of a few hundred cells isolated from the blood can hardly be expected. Such observations tend to support the thesis that there is a "natural" host resistance to cancer. Nevertheless, although autologous implantation now has only limited value for assaying the viability of tumor cells, the limitations may eventually be removed by

the discovery of techniques for extending cell survival.

The second question of major importance concerns the prognosis of patients with malignant tumors when there are demonstrable tumor cells in the blood. The studies of autologous transplantation just discussed emphasize the caution which must be exercised in attaching prognostic significance to the presence or absence of tumor cells in the blood. As might be expected, tumor cells are found in the peripheral blood more frequently when the disease is far advanced. It would be more important, however, to know the prognostic significance of tumor cells in the blood of patients with curable lesions.

In the recent report by Engell, a 5 to 9 year follow-up of his patients showed that 51 per cent of the long term survivors had tumor cells in the blood before, during, or after surgery. He concluded that these disseminated tumor cells must have perished intravascularly. This bears out many experimental observations that the majority of tumor cells injected intravenously perish on reaching the lung. Unfortunately, most of such studies were performed with transplanted tumors, and hence were not comparable to the clinical situation.

Because personal experiences have given the impression that blood-borne tumor cells are found more often in association with tumors of "greater malignancy," we are inclined to expect that future studies like that reported by Engell will demonstrate some difference in the prognosis of patients with tumor cells in the blood. Nevertheless, until more is known about the factors governing growth or rejection of blood-borne tumor cells, it would appear that there is actually no justification for attaching prognostic significance to the presence of such cells in the blood or for governing therapy by such findings.

It should be emphasized that the finding of tumor cells in the blood is absolutely not a contraindication to definitive surgery unless other evidence of incurability is present. By the same token, the demonstration that the cancer patient is capable of destroying some of his own tumor cells is no reason for changing the present standards of surgical technique and therapy for cancer, since no one can foretell the ultimate fate of a particular exfoliated cell. The advice of surgeons for many years that cancer should be isolated and treated as carefully as an infection is still germane. Certainly the various adjuvant procedures, such as preliminary ligation of the lumen of the bowel, early ligation of the vascular supply, and minimal manipulation of the tumor, should continue to be used.

Chemotherapy as an adjuvant for surgical treatment of cancer is currently under study (4). Since experiments have shown that unattached tumor cells in the blood, in body cavities, or in surgical wounds are much easier to destroy than established tumors, this new approach may well prove desirable when more effective anticancer agents become available for clinical use.

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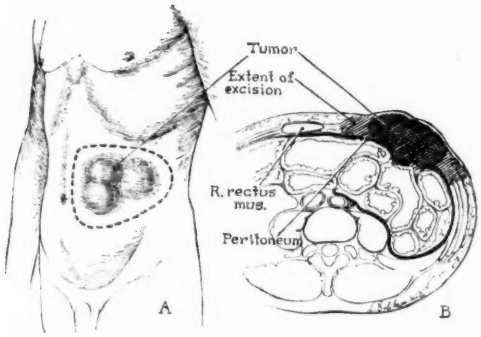

FIG. 1.

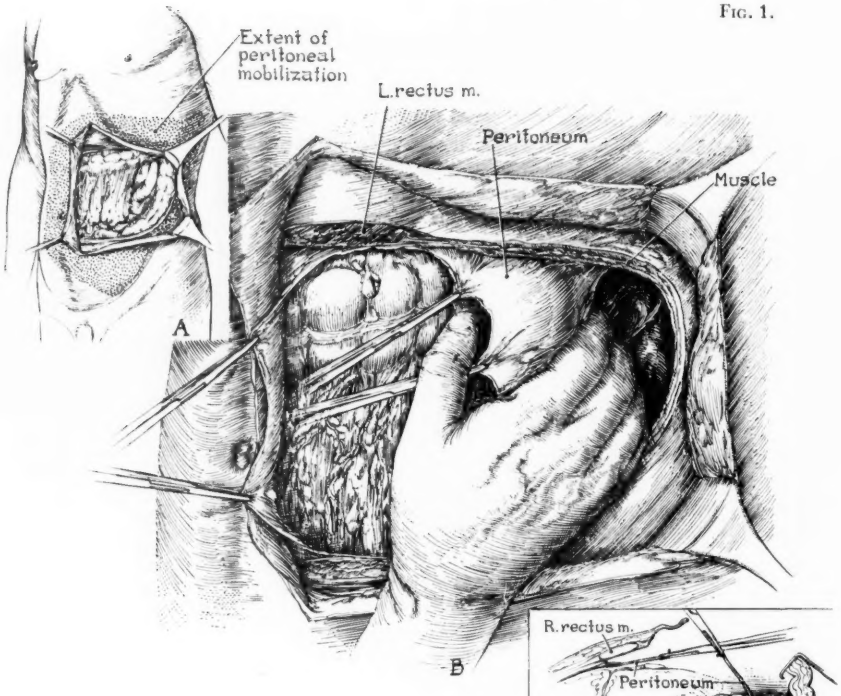

FIG. 2.

Peritoneal Reconstruction After Extensive Abdominal Wall Resection.—James R. Cantrell and J. Alex Haller.

(Legends on opposite page.)

THE SURGEON AT WORK

PERITONEAL RECONSTRUCTION AFTER EXTENSIVE ABDOMINAL WALL RESECTION

JAMES R. CANTRELL, M.D., F.A.C.S., and J. ALEX HALLER, M.D., Baltimore, Maryland

RESECTION of the full thickness of the abdominal wall is most commonly required in the treatment of malignant neoplasms. Among primary tumors occurring in this region, low grade fibrosarcomas which are locally invasive but slow to metastasize predominate. Secondary neoplasms are usually the result of direct extension of an intraperitoneal growth but may follow inadvertent implantation of tumor in the wound during resection of a primary intraperitoneal lesion. In either instance, the treatment of choice is wide local excision of the entire thickness of the abdominal wall. The peritoneum must be taken if optimal margins are to be obtained in all dimensions.

The extent of the defect created by such resections has usually been considered to preclude primary closure of either muscles or peritoneum. While reconstruction of the musculofascial defect has been simplified by the development of relatively nonreactive metallic and plastic mesh prostheses, these materials do not substitute for the smooth serous peritoneum; in fact, they present a distinct problem in this regard. Although it is acceptable to leave these materials in direct contact with the viscera, it would appear less than ideal to do so. Restoration of the complete envelope of peritoneum, thereby separating the viscera from both mesh and wound, would be distinctly preferable.

During the course of such an extensive resection of the abdominal wall, the thought occurred that peritoneal closure might be easily effected if the peritoneum were mobilized widely as is routinely done in the performance of lumbar sympathectomy and in other retroperitoneal procedures. This method has now been employed successfully in the closure of large defects in various regions of the abdominal wall and would appear to be a useful technique in the operative management of such wounds.

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CLINICAL MATERIAL

CASE 1. R. G., a 37 year old white male was admitted to the Johns Hopkins Hospital in May 1957 because of a recurrent tumor of the abdominal wall. A desmoid arising in the rectus sheath had been excised elsewhere 7 months previously, the predominant symptom being abdominal pain. Two months after the original procedure, pain returned and a mass was noticed by the patient. Because the pain had become severe further medical care was sought.

Physical examination revealed no significant abnormalities except in the abdominal region. It was noted that the left rectus incision had healed satisfactorily. Lateral to this incision and extending into the lumbar region on the left was an irregular, lobulated, hard, fixed tumor, measuring 8 by 12 centimeters in its greatest dimensions (Fig. 1A and B). It ap-

FIG. 1. Case 1. A, Extent of resection of the tumor and abdominal wall. B, Cross section at the level of the tumor showing involvement of the full thickness of abdominal wall.

FIG. 2. Case 1. A, Defect created by resection. Extent of peritoneal mobilization is indicated. B, Retroperitoneal dissection is begun at the lateral margin of the peritoneal defect. C, Cross section showing the peritoneum mobilized to the midline and rotated anteriorly and medially, leaving a retroperitoneal dead space.

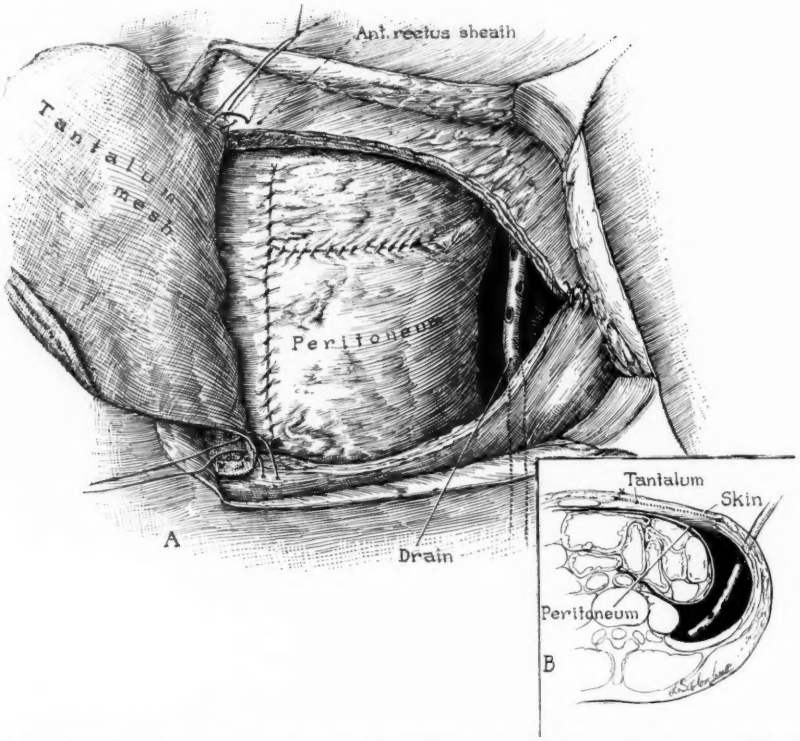

FIG. 3. Case 1. A, The peritoneum is closed primarily, a catheter inserted into the dead space, and tantalum mesh applied to the residual musculofascial defect. B, Cross section at completion of the procedure.

proached the costal margin and iliac crest at its superior and inferior margins.

It was thought that this represented a local recurrence of the tumor, and on June 6, 1957, the lesion was excised with a large segment of the abdominal wall, leaving a full thickness defect which measured approximately 17 by 20 centimeters (Fig. 2A). It seemed initially that closure of the peritoneum would be impossible, but after further consideration it appeared that extensive mobilization in the retroperitoneal plane might provide sufficient mobility to allow primary suture. Dissection was begun at the lateral margin of the peritoneal defect (Fig. 2B) and carried posteriorly to the vertebral column (Fig. 2C), superiorly to the diaphragm, and inferiorly to the pelvis. This mobilization allowed sufficient medial rotation of the peritoneum to permit primary suture without tension (Fig. 3A). A large retroperitoneal space resulted which extended almost to the diaphragm and into the lateral pelvis. A single multiperforated catheter was inserted into this space and brought out through a stab wound in the abdominal wall just above the midportion of the inguinal ligament (Fig. 3B). The defect in the abdominal wall was closed with a large sheet of tantalum mesh, and the skin was approximated over the mesh.

The catheter was attached to constant gentle suction at the conclusion of the procedure. A moderate amount of serosanguineous drainage persisted for 24 hours; suction was discontinued after 48 hours. The postoperative course was uneventful and the patient was discharged on the seventh postoperative day. Histologic study of the specimen confirmed the impression of fibrosarcoma.

CASE 2. R. R., a 50 year old white male, was first admitted to the Johns Hopkins Hospital in November 1958, because of a painful mass in the left lower quadrant. Six years prior to admission a Mikulicz resection of the colon had been carried out elsewhere for adenocarcinoma of the sigmoid. The colostomy was closed after several weeks. He remained well until several months prior to the present admission when he began to note severe, intermittent pain in the left lower quadrant. One month prior to admission he noted a mass just medial to the anterior superior iliac spine beneath the old incision.

Physical examination revealed an 8 by 11 centimeter, hard irregular mass in the left lower quadrant of the abdominal wall (Fig. 4). The mass, which lay beneath the surgical incision, was fixed to the anterior superior iliac spine but was not adherent to the skin. Results of examination were otherwise negative.

Complete study revealed no other evidence of recurrent tumor.

It was believed that this lesion represented a local recurrence of the sigmoid carcinoma, probably the result of direct wound implantation at the site of the colostomy. On November 11, 1958, the lesion was excised with a 4 centimeter circumferential margin. The full thickness of the abdominal wall was resected in continuity with the anterior superior spine of the ilium and the upper third of the inguinal ligament. The resulting defect extended medially to the midportion of the rectus muscle, laterally to the midaxillary line, and inferiorly to within 5 centimeters of the pubis. By mobilizing the posterior peritoneum to the vertebral column and sacrum medially, deep into the pelvis inferiorly, and to the diaphragm superiorly, it was possible to displace the viscera medially and to approximate the edges of the peritoneal defect with a continuous suture of No. 00 chromic catgut. The lateral space created by this rotation was drained by a single catheter. The muscular defect was closed as completely as possible, and the remaining 12 by 13 centimeter defect was covered with tantalum mesh. The skin was closed primarily. Histologic study of the lesion revealed metastatic adenocarcinoma. No other residual tumor was noted during the course of laparotomy.

The postoperative course was uneventful. Constant suction was applied to the catheter; drainage ceased after 48 hours and the catheter was removed after 72 hours. The patient was discharged from the hospital on the tenth postoperative day.

CASE 3. M. O., a 46 year old colored male, was admitted for the excision of a 4 by 5 centimeter tender, firm mass in the left rectus muscle, 4 centimeters below the costal margin (Fig. 5). A complaint of epigastric cramping pain of 6 to 8 weeks' duration suggested either intra-abdominal origin or extension of the mass. Results of gastrointestinal series and barium enema, however, were negative.

On January 12, 1959, excisional biopsy of the mass was performed. It was found to lie within the rectus sheath and frozen section revealed a desmoid tumor. Accordingly, an en bloc resection of a 7 by 10 centimeter portion of anterior and posterior rectus fascia, rectus muscle, and peritoneum was performed. Lateral mobilization of the peritoneum to the posterior axillary line allowed closure of the peritoneal defect with mattress sutures of silk. The musculofascial defect was covered with knitted teflon mesh, and the subcutaneous tissue and skin were closed with silk. Except for the accumulation of a small amount of subcutaneous fluid which required aspiration, the patient's course was uneventful.

DISCUSSION

When resection of the full thickness of the abdominal wall requires the use of prosthetic material for repair of the musculofascial defect, it would seem theoretically advantageous to interpose peritoneum between the prosthesis and viscera. At least three practical considerations support this thesis.

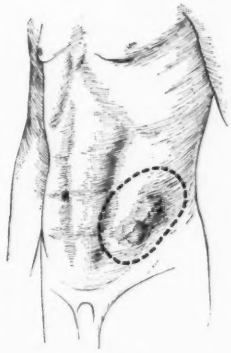

FIG. 4.

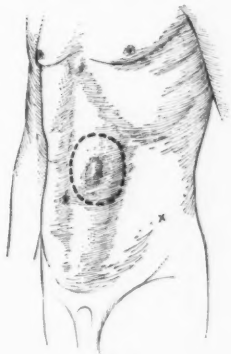

FIG. 5.

FIG. 4. Case 2. The lesion and extent of resection.
FIG. 5. Case 3. The lesion and extent of resection.

1. Development of adhesions. In a limited number of cases in our own experience and in the patients reported by Koontz (1) and Stafford in which tantalum mesh had been placed in direct contact with the viscera, relatively short follow-up suggested that such contact could not be considered to be a distinct contraindication to the use of mesh. The experimental studies of Koontz (2) and Pearce, however, have revealed certain disconcerting sequelae; bowel and mesh were noted to have become diffusely adherent by fibrinous adhesions within 24 hours. These adhesions persisted and observation after 6 months revealed them to be both extensive and dense with attenuation into bands of the type which are commonly associated with the development of intestinal obstruction. In this regard, the generally propitious property of tantalum to incite fibrous tissue reaction would appear disadvantageous. Certainly, such bands constitute a serious potential hazard. While adhesions may indeed develop despite all possible precautionary measures, peritoneal closure will at least minimize this process and its possible complications.

2. Fluid collection. Wounds resulting from such extensive resections invariably produce a significant quantity of serosanguineous fluid which requires either drainage or multiple aspirations. It is, unquestionably, preferable to isolate the peritoneal cavity from the source of this fluid. The development of infection within the wound would be particularly serious if the wound remained in direct contact with the viscera.

3. Erosion of viscera. It would appear that the late fragmentation invariably observed in the case of tantalum mesh is unlikely to result in erosion of the bowel. Even though contact is intimate, the fibrous reaction incited by the mesh is probably sufficient to sheathe the resulting sharp metallic ends and prevent injury. Stainless steel mesh, on the other hand, does not produce such a marked reaction, and the possibility of erosion and perforation may exist. The plastic fabrics, of course, are not subject to such difficulty.

Closure of the peritoneum without tension is feasible even in extensive defects if adequate mobilization is carried out.

Conceivable disadvantages of such mobilization are: (1) the rather refractory paralytic ileus frequently seen after extensive retroperitoneal procedures and (2) the dead space created by the reduction in volume of the peritoneal sac. Ileus has not been a problem in the patients thus far treated. The dead space is apparently rapidly eliminated by catheter suction; it seems likely that the highly flexible peritoneum easily stretches to accommodate to the size of this space.

This technique would appear to obviate some of the difficulties inherent in extensive resection of the full thickness of the abdominal wall. It is an innocuous and technically simple procedure and has been shown to be effective in defects of the upper, middle, and lower abdomen. It will presumably be applicable to all defects of the abdominal wall, regardless of location.

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STERILITY IN OPERATING ROOMS

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THIS ARTICLE is the seventh in a series published during the past 3 years reporting investigations into the causes of wound infection at Huggins Hospital, and the methods of prevention. Concern arose in 1956, when the infection rate in clean wounds mounted to 1.4 per cent for the year. Although never again approximated as a figure of incidence, probably because of the exacting routines instituted, sporadic infections continued to occur. It was realized that surgical technique, at least in our hands and experience, simply could not be made sufficiently meticulous and careful to avoid occasional bacterial implantation from sources of fomites, infected air droplets, and contamination from personnel.

Fifteen months ago, it was demonstrated that any area whatsoever could be rendered nearly sterile by sufficient mechanical cleansing and by the application of a detergent-disinfectant solution, by isolation, and by protection when these were applied to an entire operating suite, and to every surface, article, and all of the contents within it. At the end of 12 months, there had been 2 clean wound infections in 800 cases, 0.25 per cent.

We believe that most wound infections originate in the operating pavilion, and that exacting attention should be given to the multiple details of surgical technique. We also believe that protection against wound infection can be provided by excluding bacteria from the environment surrounding an open wound.

This investigation is based upon the premise that sterility in operating rooms is a desirable end to achieve, and that modes of bacterial transmission are recognizable and definable. A method of maintaining cleanliness that works in practice is described. In our hospital, the described routines are followed regularly and rigidly, by everyone without exception. These procedures of necessity are simple and sensible in order to be practical and effective in daily clinical practice. The routines are definite and exact, from years of revision and improvement in procedures, as indicated by frequent analysis of the constantly accumulating data. The manner and the extent of descriptive detail given not only reflect actual experience in the pavilion, but also provide the answers to more than 9,000 questions asked regarding this work in the past 3 months. An estimated 90 per cent of these questions fall into 30 categories, and the total number of questions fall into less than 50 categories.

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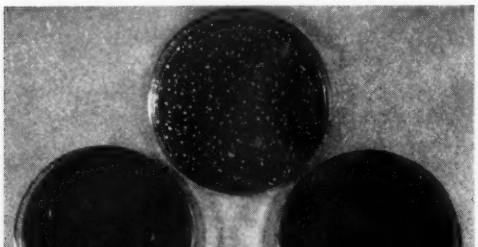
ATTAINING STERILITY

Floors, walls, and furniture in operating rooms and corridors are exposed constantly to contamination. Sterility of such surfaces is attained by scrubbing with a disinfectant-detergent solution, changed frequently during application. Unless scrupulously protected, the floors and walls of an operating pavilion will show contamination identical to that of a public corridor. The problem as it exists in an unprotected operating room is illustrated in Figure 1.

As previously demonstrated by us as well as by Walter and associates, any surface whatsoever can be made clean and even sterile by the adequate application of the cleansing process. In or-

FIG. 1. Culture of second floor corridor adjacent to operating room pavilion.



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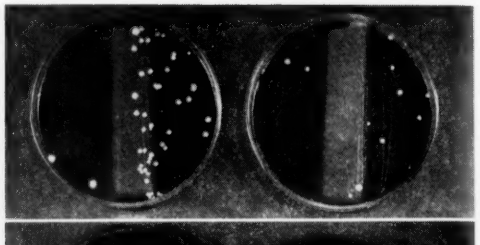

b

FIG. 2. a, Swab type cultures: top, second floor corridor outside operating room pavilion; lower left, operating room pavilion interchange area cleaned hourly—no restrictions on use of area; lower right, operating room pavilion interchange area 5 minutes after cleaning. b, Top, contamination of mechanically clean area by use of contaminated cleaning cloth; bottom, culture from same area after recleaning with germicidal agent.

der to obtain such results, a worker intent in doing a vigorous manual cleaning job is a requisite. Simple buckets, cloths, and mops should be provided that can be autoclaved as a unit after each period of usage. Necessary equipment includes a mop with a built-in squeegee or a wet pick-up microstatic filter protected vacuum cleaner. Generous supplies of hot water mixed with a detergent-germicide solution should be used, and this solution should be changed as often as it begins to look soiled. The worker must himself be clean, so as not to recontaminate while decontaminating. Such activity will routinely render a surface or area nearly sterile, even in the presence of very extensive use. By example, as shown in Figure 2a, the floor of the operating pavilion interchange can be kept essentially sterile during heavy unrestricted use, by hourly cleaning with a fresh clean mop and a fresh detergent-germicide solution. A public corridor located only 6 inches away, separated by a closed door and bearing a similar load of traffic but not subjected to protective cleaning, remains greatly contaminated.

Mechanical cleanliness may be accompanied by bacteriologic dirtiness, as shown by the pair of duplex cultures in Figures 2b. The 2 cultures illustrated in the upper portion of the photograph were taken from tabletops which were as clean mechanically as they could be made by diligent effort. They were bacteriologically contaminated when the clean surfaces were wiped with a cloth that had been standing in a spent and grimy disinfectant solution. Wiping of the mechanically clean surfaces with fresh disinfectant solution cleared the surfaces so that cultures then yielded no growth, as shown by the 2 petrie dishes in the lower part of Figure 2b. This indicates that anything which is mechanically clean can be rendered sterile easily by an effective disinfectant.

By contrast, sterility is almost impossible to attain on a surface that has not been mechanically cleaned. A shoe which had been soaked for 1 hour in a freshly made strong germicide solution, but the surfaces of which were not totally free of particulate matter, was subjected to culture by swabbing and a heavy bacterial growth was obtained. When this experiment was repeated using all of the germicides commonly used in hospitals the results were identical. Therefore, any surface which has not been mechanically cleaned cannot be rendered reliably sterile by the use of any germicide, no matter how strong or how long it may be applied. Again, in contrast, a culture was taken from a mop pail which a cleaner had used for an hour, and with which he planned to "clean the operating room floor." A solid overgrowth of a mixed flora was produced. This proves, therefore, that mops and pails must be autoclaved and that detergent-germicide solution must be changed for each room.

MAINTAINING STERILITY

The preceding section was devoted to measures for making sterile, or nearly so, all surfaces in an

operating room, whether floors, walls, furniture, equipment, or fixtures. This section is devoted to maintenance of sterility. The problem of room air sterility is not easily categorized as one of attainment or of maintenance, but is simply achieved and easily continued. An air-conditioning system should deliver under positive pressure a volume of air sufficient to cause a complete exchange every 4 to 12 minutes, depending upon the amount of occupancy. The final phase of the filter system should include a feature which is described variously as "ultimate," "deep-bed," "precipitation," and "microstatic" filtration. Any one of these systems will deliver to the entering ducts air which is essentially sterile and contains no particulate matter larger than 0.3 micron. The bacteriologic effectiveness is near total because of the fact that staphylococci and most other pathogenic bacteria have dimensions larger than will pass through such filters. The outward air pressure must be such that a ribbon hanging on the portal will not deflect inward when a door anywhere in the operating pavilion is opened in either direction. The air-conditioning system described is portrayed diagrammatically in Figure 3.

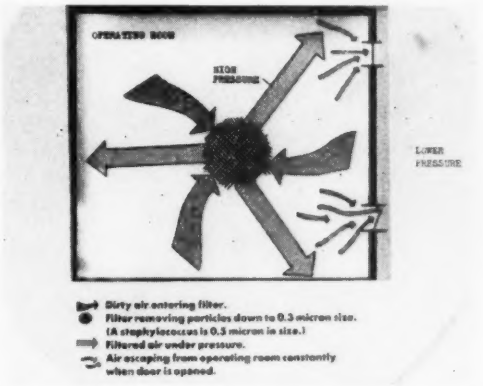
OPERATING ROOM
HIGH PRESSURE
LOWER PRESSURE
Dirty air entering filter.
Filter removing particles down to 0.3 micron size.
(A staphylococcus is 0.3 micron in size.)
Filtered air under pressure.
Air escaping from operating room constantly when door is opened.

FIG. 3. Scheme of air treatment, 1 air change every 4 minutes, and distribution in use at Huggins Hospital operating rooms.

Near sterility of operating rooms, having been attained by the measures outlined in the preceding section, can be maintained indefinitely by the constant application of the following three principles:

1. The cleaning process must be repeated frequently, using a detergent-disinfectant solution. It is our policy to repeat the cleansing process after each operative procedure, which includes the washing down of walls from a height of 6 feet to the floor, washing of the floors of the operating room used, the scrub-up, exchange, and interchange areas. The furnishings and equipment are rubbed down with the detergent-disinfectant solution. The completion of this process requires 20 minutes for 1 man and 1 woman. This should be a clean sweep procedure, starting at the rear with all furniture moved forward. When completed, all floor and furniture surfaces are clean.

2. The operating pavilion must be isolated by physical barriers from the rest of the hospital. The concept of protection for the open wound by sterile drapery and nurses table, and circulating nurse with transfer forceps, has been extended to the operating pavilion. It is called the "concept of zones" and may be fully understood by reference to Figure 4, in which bacteriologic culture plates have been arranged and labelled in accordance with the rooms, areas, or zones which they represent. An exchange area is one between that which is dirty or contaminated and that which is clean or sterile.

3. Surfaces which cannot be sterilized must be bacteriologically protected. This principle has been observed by generations of surgeons as they have applied protective toweling around the sterilized area selected for incision. This principle has been extended to the attire and skin of personnel and patient, for reduction of infection hazards from these two prime sources of contamination in the operating room. That which cannot be cleaned up should be wrapped up.

PROTECTION OF ENVIRONMENT

Protection of the environment against contamination by personnel or the patient is achieved in many ways. All details are important, in that failure in the performance of one item can cause trouble for the whole system. By analogy, a gas line which is perfect except for one hole through which it leaks is an intolerable gas line.

Freshly cleaned coverings and a mask are placed upon the patient at the door of the interchange area, where carts are exchanged for his conveyance into the operating room.

Operating pavilion entry at any time by any member of the personnel is permitted only when they are properly cleaned and when covering apparel is worn. Our studies have been accompanied by an invariable policy of revealing the

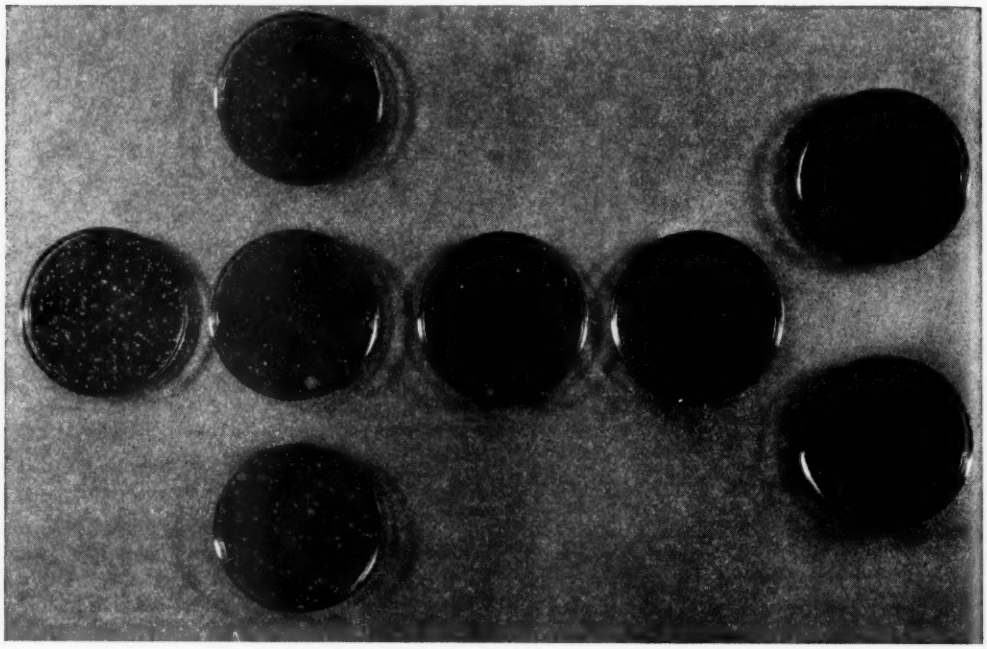

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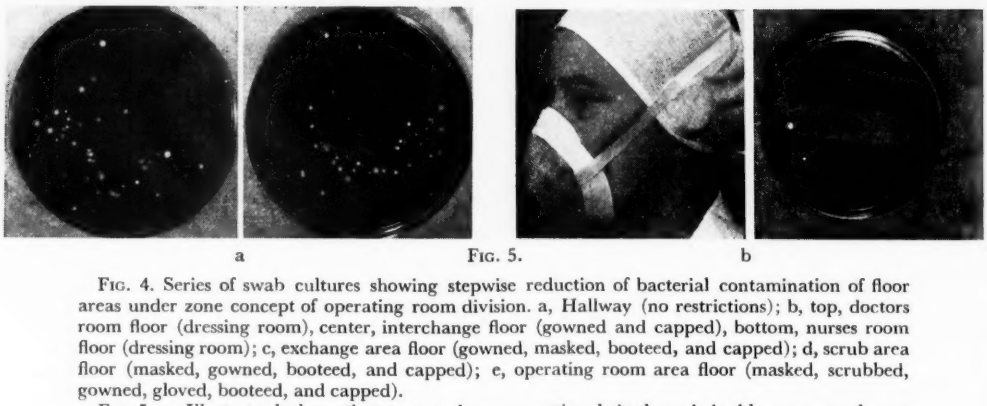
FIG. 4.



a b

FIG. 5.

FIG. 4. Series of swab cultures showing stepwise reduction of bacterial contamination of floor areas under zone concept of operating room division. a, Hallway (no restrictions); b, top, doctors room floor (dressing room), center, interchange floor (gowned and capped), bottom, nurses room floor (dressing room); c, exchange area floor (gowned, masked, booteed, and capped); d, scrub area floor (masked, gowned, booteed, and capped); e, operating room area floor (masked, scrubbed, gowned, gloved, booteed, and capped).

FIG. 5. a, Illustrates leakage that occurs when conventional single and double gauze masks are worn (slit sample ½ hour plate). b, Model wearing new type mask. Swab culture of outer surface of new type filter mask after operation.

results from tests to the entire staff, from humblest maid to chief administrative officer, with explanation of meaning as the data were accumulated. Thus, when the necessity of shoe coverings was recognized as the only practical means for bacteriologic protection of the pavilion against this source of contamination, there was no question about whether bootees would thenceforth be worn, and changed for each re-entry. Neither has anyone assumed that his own shoes are sterile as opposed to those of others.

The most frequent question asked was posed in many forms but may be accurately phrased as follows: "What do you do about the renegade

surgeon who assumes himself to be sterile of breath, skin, clothes, and shoes, fertile in the wisdom of his own unmasked running commentary, and scintillating in his sarcasm for those who interpret welfare of the patient as including protection against infection during operations?" Fortunately, we have had no surgeon of this type with which to deal. So strong is the power of group opinion, that one cannot imagine any surgeon brazen enough to absorb the derision of maids, cleaners, orderlies, nurses, and staff while using his rank to destroy such protection which all of that group are so dedicated in maintaining.

Clothing that is to be worn during operation should be as clean and as dry as possible when covered by the sterile gown. The use of an impervious apron during the scrub-up with removal immediately prior to operating room entry has proved helpful in preventing scrub gown contamination by droplets from the scrub brush.

STERILIZATION AND ISOLATION OF SKIN

Skin preparation should include sterilization and isolation for both personnel and patient. Both hand washing and the wearing of surgical gloves—isolation—have been long accepted as routine by surgeons and nurses alike. Although never beguiled into the "quickie scrubs" as advocated a few years ago using certain detergents, popular with the lazy, we have conducted scores of tests on relative efficiencies of different methods, soaps, detergents, and rinses. The simplest routine of producing uniform sterile skin on hands day after day for most individuals is herein outlined, and has been the ritual used for more than a year in our operating rooms.

The technique for hand scrubbing is as follows: Put on a clean, impervious apron and then: (1) Wash hands and arms with hot water and detergent-antiseptic solution vigorously for 1 minute and rinse well with clear, warm water. (2) Scrub vigorously with a sterile brush and detergent-antiseptic solution for 4 minutes, rinsing frequently, and then dispose of the brush. (3) Take a new sterile brush and scrub for a second period of 4 minutes, applying the detergent-antiseptic frequently, scrubbing, and rinsing. (4) Use the antiseptic solution as freshly provided, and rinse hands and arms repeatedly for 1 minute, allowing the solution to drain off from the elbows into the scrub sink. (5) Have apron removed by the attendant. (6) Enter the operating room and have a nurse provide a sterile towel for drying the hands.

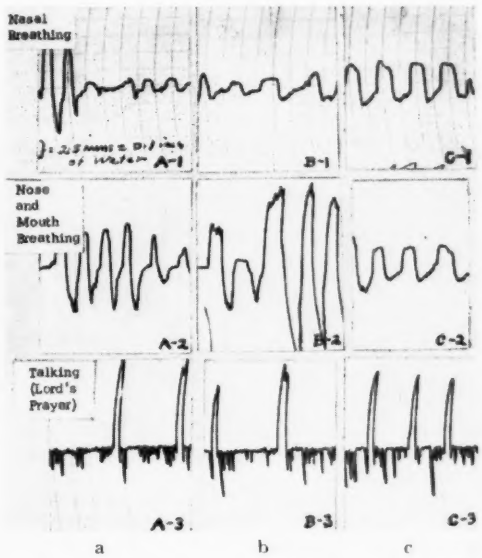


FIG. 6. Comparison of resistances encountered when, a, single, b, double gauze masks and, c, filter masks were worn during nasal breathing, nose and mouth breathing, and while talking. Polygraph measurements.

The skin of the patient presents the same hazards. Therefore, it is given identical treatment. This is best done in the patient's room, but it may be done in the operating pavilion. Plastic sterile film made adherent to the skin is equivalent in effectiveness to the rubber gloves worn by surgeons and assistants. When properly applied it will protect against skin contamination from the patient in a manner identical to that in which gloves protect him against contamination from the hands of personnel.

An allegation of spark hazard from the plastic has been thoroughly investigated, and detailed findings have been reported elsewhere. In summary of the findings herein one need report only that engineers, recognized as experts in respect to their knowledge and experience with static electricity, have been unable to derive a spark from the material, either in our operating rooms or under the most nearly ideal conditions they could set up in static electricity research laboratories for production of spark. It is our opinion that the spark risk from proper use of this plastic film is zero.

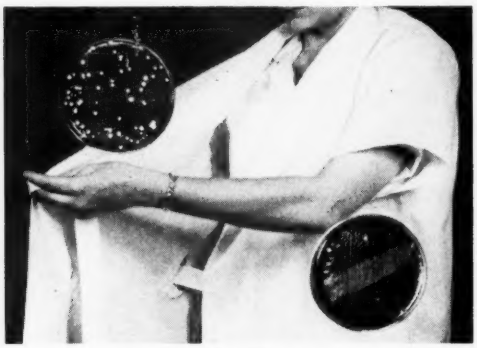


FIG. 7.

FIG. 7. Wrap-around type of gown. Plate insert, above, culture of surgeon's clean pant leg after short usage; below, culture of wrap-around gown as received from commercial laundry.

FIG. 8. Bootee for shoe covering. Above, culture from surgeon's shoe; below, culture of freshly laundered bootee.

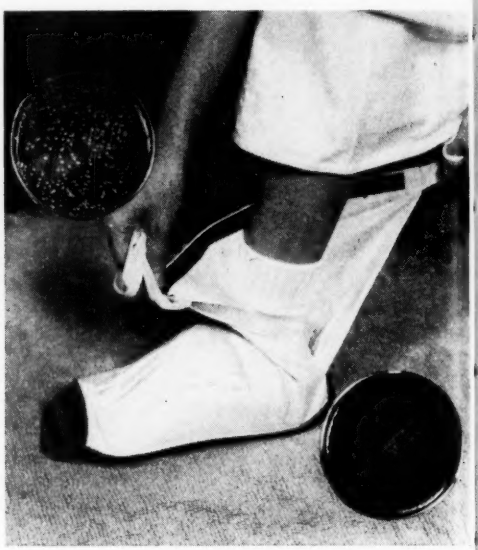


FIG. 8.

WEARING OF PROPER ATTIRE

If there were no people, there would be no problem, even of attaining and maintaining sterility in operating rooms. From a less philosophic, but more practical viewpoint, the people, meaning personnel and patient, infect an operating room environment by exhaling bacteria into its air through inefficient masks, by shedding germs from their skin and clothing, and by tracking in contamination on their dirty shoes. These methods of introducing infection are so time-honored as breaches in the observance as to have become ritualistic symbols to many surgeons and institutions. They have, bacteriologically speaking, a meaning equivalent to the unkempt frock coat and wallhung needle cushion of a surgical era perpetuated only by archives.

The minimum requirements for proper surgical attire are: (1) a fitted filter mask, (2) a quick change wrap-around gown put on freshly clean for each operating room entry, (3) bacteriologically protective conductive booties for coverage of shoes.

The principle of the fitted filter was applied to surgical masking because of a continued efficiency of above 95 per cent. Since the filter porosity will not allow transmission of particles larger than 0.3 micron, the efficiency of the filter material itself for trapping of bacteria is almost perfect, most pathogenic bacteria being larger than 0.5 micron. Careful adaptation to facial skin contours allows one to apply this high efficiency to the filtration of bacteria from exhaled air. The manner of wearing a fitted filter mask is shown in Figure 5 and its superior efficiency is demonstrated by the culture plates which are compared with those taken when single gauze and double gauze masks were worn.

An efficiently fitted filter mask is equally as comfortable as any other type and lack of interference with visibility is also equal. The third most often raised question about fitted filters is in regard to differential pressures against atmospheric pressure. Figure 6 shows pressure data in detail for single gauze, double gauze, and fitted filter masks, and under conditions of quiet breathing, open mouth breathing, and upon speaking. As may be seen, all produce average breathing pressures of less than 0.5 centimeter of water, and responses to equal situations are comparable within 3 millimeters of water pressure. Although the actual differences in weight, comfort, visibility and breathing pressure are very small, psychologic reactions often are pronounced, particularly in older individuals. These are transient and disappear within a few days, and are not a barrier to acceptance of the far greater efficiency of bacterial protection by those concerned.

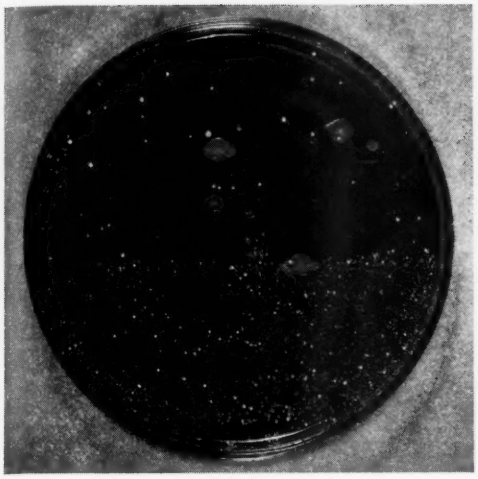


FIG. 9.

FIG. 9. Lower portion of plate, culture of scrub area floor after 1 hour of use; upper portion of plate, culture of materials used in scrub area after 1 hour of use.

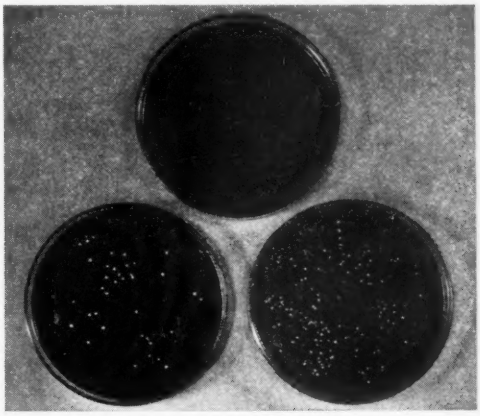


FIG. 10.

FIG. 10. One hour slit sampler plate showing effect on air counts when improperly fitted masks were worn. Top, culture from operating room, no activity; below, left, operating room, activity; below, right, scrub area.

The ease with which clean clothing becomes contaminated by bacteria when exposed to a germ laden environment is surprising. Figure 7 clearly demonstrates this fact. The heavily contaminated culture, top left, is from the scrub suit of a surgeon, who put it on clean and then went out into the ward for 5 minutes before reentering the operating room. The culture at the bottom, right, with practically no growth, was taken from the outer surface of identical clothing which the same individual had put on and then entered a bacteriologically isolated operating room. The ease and bacteriologic safety with which double breasted wrap-around gowns can be changed, as contrasted to blouses pulled on over dirty hair or trousers pulled on over dirty shoes, have caused our group to adopt this easier, safer, more satisfactory method of garbing the torso, for both male and female.

Since there is no practical alternative thus far developed, shoes that are to be worn into an operating room must be cleanly wrapped-up immediately prior to entry. Freshly laundered conductive bootees which come above sock or anklet level and cover the shoe and sock completely, making conductive rubber electrical contact with the skin of the wearer, have proved to be very satisfactory for this purpose. The cultures made from the bootee illustrated in Figure 8 show the necessity of freshly clean shoe coverage for each reentry. A culture was made from a surgeon's shoe at pavilion entry, and the heavily laden mixed flora plate (Fig. 8, above left) of the shoe resulted from swabbing of the sole. The nearly barren culture plate (Fig. 8, below right) shows the condition of the sole of a freshly laundered bootee as the wearer entered the operating room.

For the reasons demonstrated, we are convinced that only personnel who are cleanly and freshly garbed, masked, and shod should be allowed into operating rooms.

CLINICAL EFFECTS

If one does not enforce protective measures for an operating pavilion that has been brought to a condition of near sterility, the high level of efficiency can be lost within an hour. Figure 9 shows the effect of allowing carelessly garbed and masked personnel to enter a scrub area.

The problem of bacterial recontamination in operating rooms which have been made clean is essentially one of human activity. This fact is portrayed in Figure 10, which shows the rapid build-up of bacteria in the air which occurred from a group of personnel because of many but minor deficiencies in the application of protective measures. For some time it was believed that wherever people were present build-up of bacterial flora could not be prevented from occurring. Figure 11 demonstrates that such a pessi-

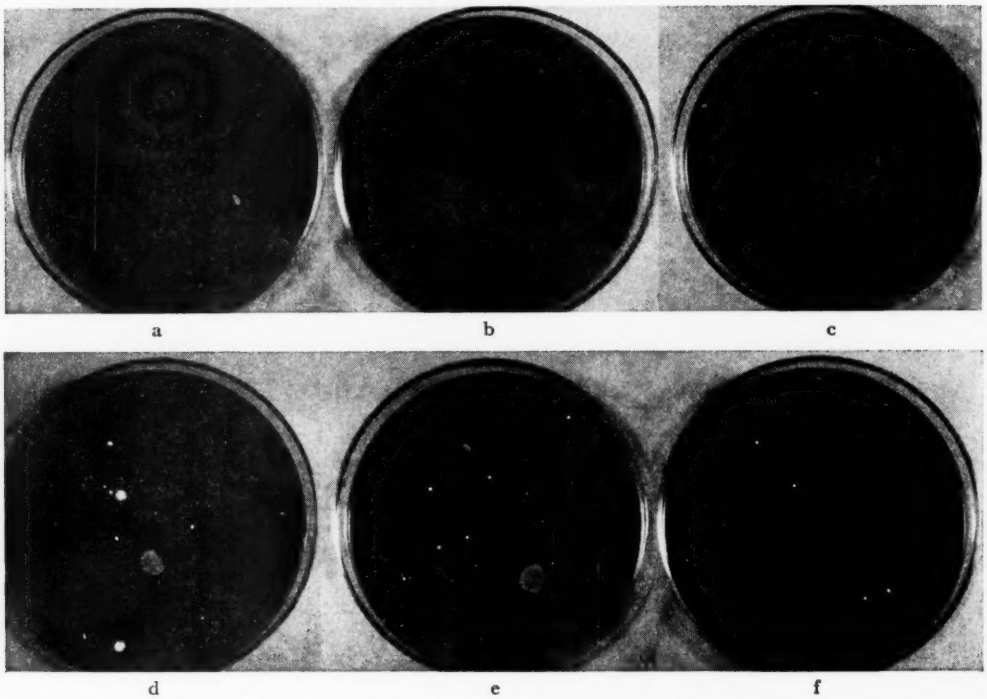


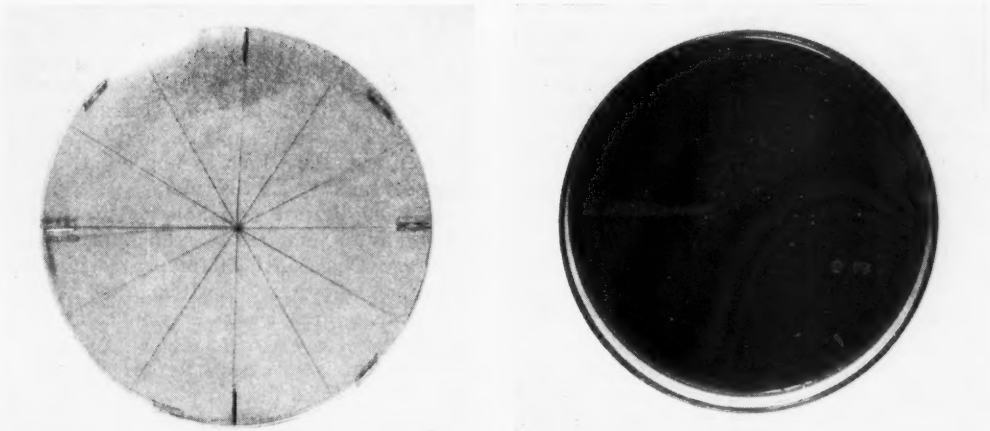
FIG. 11. Series of 6 one hour slit sampler plates taken before, during, and after 3½ hour gastrectomy. Illustrates value of properly fitted and worn operating room pavilion attire. a, First hour, no activity; b, second hour, operating room being set up for gastrectomy; c, third hour, preparations complete, operation in progress, three people in area; d, fourth hour, operation in progress, 7 people in area; e, fifth hour, operation in progress, 8 people in area; f, sixth hour, operation completed, operating room vacant last 20 minutes.

mistic viewpoint is not necessary, at least from a practical viewpoint. These slit sampler cultures were taken continuously and consecutively for 6 hours, 1 cubic foot of room air per minute passing steadily over the plate. The fact that contamination bears a direct relationship to activity is confirmed, but the demonstration is also clearly made that 8 people can be in an operating room for a long and difficult operation over the course of many hours, with maintenance of a high degree of bacterial protection. The clinical effects of this infection control program have been near total sterility in operating rooms all day, every day, and a reasonably low incidence of clean wound infections (0.25 per cent).

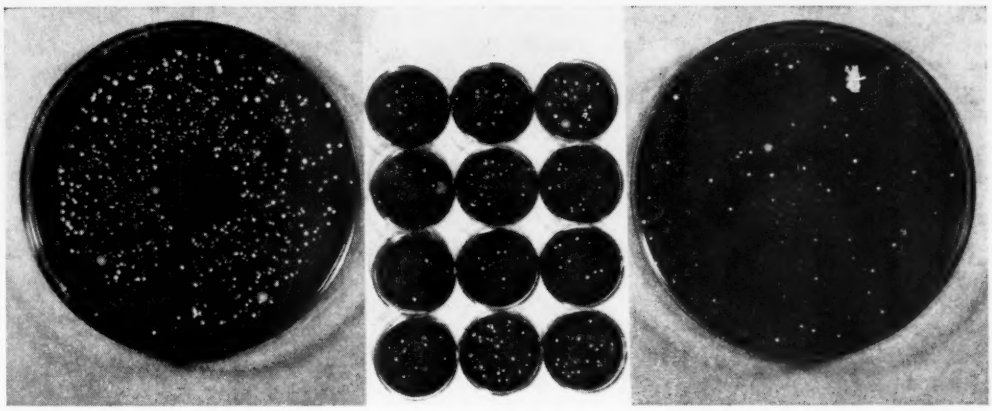
SAMPLING METHODS

Bacterial contamination of air may be measured by any of the following methods: gravity plate, membrane filter, sieve sampler, slit sampler, and Wells air centrifuge. Of these, either the slit sampler or the Wells air centrifuge is the most satisfactory and reliable to use.

The gravity plate method recovers only about 10 per cent of the total bacterial counts when compared to data obtained using a slit sampler. Membrane filters used for a prolonged period of time i.e., 1 hour, obtained air counts that were lower than any known to exist. This is probably due to the desiccation of vegetative bacterial forms by the volume of air flow through the filter. In either the sieve, slit, or Wells air centrifuge methods, bacteria are impinged directly on a nutrient material, and the growth of the organism may commence at once. Disadvantages with the sieve sampler method are the frequency of change of plates—every 5 minutes—and the piling-up effect caused by one organism being deposited on top of another already impinged on a nutrient material. Erroneously lower counts



a FIG. 12. b



a b c

FIG. 13.

FIG. 12. One hour slit sampler study moved 16 times in 1 hour to illustrate lack of effect caused by turbulence and positioning. a, Grid designed to evaluate plate.

FIG. 13. Comparison of plates simultaneously obtained by 1 hour exposure in the same area. a, Slit sampler; b, sieve sampler; c, gravity plate. Note remarkably higher counts obtained by slit sampling from same area as the other two methods.

are yielded. Slit sampling has the advantage that it can be run for 1 hour without a plate change as well as that the organisms are deposited on a fresh nutrient surface during every second of the entire period. The Wells air centrifuge presents the same advantages of the slit, with the additional feature that any clumps of bacteria are deposited as a unit and are not dispersed, it being held that a clump of organisms represents only one infecting entity rather than the sum of the number of viable organisms present in the clump. Data obtained from slit sampling and Wells air centrifuging compare most favorably.

The slit sampler was used with the flow of air regulated at 1 cubic foot per minute, each plate representing 60 cubic feet of air per hour. One hundred and fifty millimeter sized petrie dishes were used. Nutrient substrate was prepared, using blood agar base enriched with 3 per cent defibrinated sheep blood. Eugenic growth of all organisms was produced when incubated at 37 degrees for 36 to 48 hours.

Air turbulence in positioning of the slit samplers was carefully studied. No effect could be detected on the plate counts regardless of the positioning or of the amount of air turbulence, so long as the environment remained constant and protected in all instances. Figure 12 demonstrates the lack of effect that turbulence and positioning create. Figure 13 illustrates the various methods of sampling and the results of each.

RESULTS

Beyond the immediate clinical results just stated, there are collateral effects from such a program which cannot be disregarded. Every major infection costs someone $3,000. In some series, infection rates were reported as 50 per 1,000 (5 per cent), or more, and 2 per cent is considered by many hospitals as a maximum beneath which to keep. An infection rate of 50 per 1,000 at a cost of $3,000 per case means an expenditure of $150,000 per 1,000 cases. This infection control system reduces the rate to 2 in 800 cases, 0.25 per cent, which equals $7,500 per 1,000 cases. The extra work to achieve this result costs less than $6,000. Thus, there was a saving of $136,500 per 1,000 cases indicated.

SUMMARY

Floors, walls, and furniture in operating rooms and corridors are exposed constantly to contamination. Sterility of such surfaces is attainable through scrubbing with a disinfectant-detergent solution, changed frequently during use.

Sterility in operating rooms can be maintained solely by frequent repetition of bactericidal cleaning processes, isolation by physical barriers from the rest of the hospital, and bacteriologically protective coverage of surfaces which cannot be sterilized.

Protection of environment against contamination by patient and/or personnel is achieved by using freshly clean coverings and mask on the patient at the door of interchange for operating room entry, by admitting to the operating room at any time only those personnel wearing properly cleaned covering apparel, and by wearing protective clothing such as impervious aprons during 10 minute hand scrubup.

Skin sterilization and isolation are accomplished by a 10 minute skin scrub plus antiseptic, coverage of personnel with proper masks, sterile gowns, and gloves, and isolation of the patient's skin with sterilized, transparent, adherent plastic skin drapes.

Minimum requirements for proper surgical attire are a fitted filter mask, a quick change wrap-around gown put on freshly clean for each operating room entry, and bacteriologically protective conductive bootees to cover the shoes.

Clinical effects of this infection control program are near-total sterility in operating rooms all day, every day—2 infections of clean wounds in 800 cases.

Every major infection costs someone $3,000. An infection rate of 50 per 1,000, or 5 per cent, which equals $150,000 per 1,000 cases has been reported in some series. This infection control system reduces the rate to 2 in 800 cases, or 0.25 per cent, which equals $7,500 per 1,000 cases. The extra work involved to achieve this result costs less than $6,000. Thus, there is a monetary saving of $136,500 per 1,000 cases.

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THE SAPHENOCAVAL APPROACH FOR POSTOPERATIVE CATHETERIZATION OF PORTACAVAL SHUNTS

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ONE PROBLEM in the management of patients undergoing portacaval anastomosis is the postoperative evaluation of the effectiveness of the shunting procedure. In a study of patients who have had side-to-side portacaval shunts for bleeding esophageal varices, information was required regarding the patency of the anastomosis, the free portal vein pressure, the intrahepatic pressure as obtained by wedged hepatic and wedged portal vein pressures, and oxygen saturations of the blood from both the hepatic and portal venous radicals (2). The technique to be described was utilized in 7 such patients and has proved to be a simple method in evaluating the functional result of shunting procedures.

TECHNIQUE

With the patient in a fasting condition and lightly sedated, the region of the right saphenofemoral area is exposed under local anesthesia. The saphenous vein or one of its major branches is isolated and prepared for insertion of the catheter. A No. 7 or 8 cardiac catheter is then inserted into the vein and advanced into the inferior vena cava. A pressure determination is made in the inferior vena cava, and all other pressures are related to it, thus minimizing errors due to variations in base line and to fluctuations in venous pressure. Under fluoroscopic control, at a level judged to be near the anastomosis, the catheter is manipulated until it can be seen to leave the vena cava (Fig. 1). The course of the catheter and its wedged position are of importance in determining whether the catheter has passed through the portacaval anastomosis, into a hepatic vein, or into a renal vein. Figure 2 demonstrates the typical position for an intraportal catheter; Figure 3 demonstrates a subdiaphragmatic approach of the catheter after entering the right hepatic vein. In Figure 4, a more sharply angulated straight approach is shown which occurs with catheterization of the renal vein.

After the catheter has been satisfactorily introduced into the portal vein, the free portal pressure is determined and compared with that of the inferior vena cava. After the free portal pressure has been recorded, the catheter is then advanced into a portal venule until the size of the vessel obstructs its passage. The wedged portal pressure so obtained reflects the intrahepatic sinusoidal pressure and is similar, in

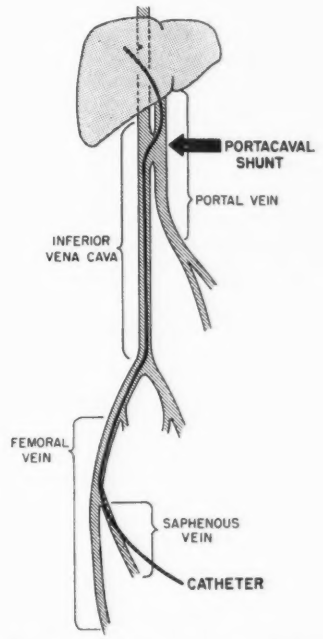

FIG. 1. The course of the catheter passing through the anastomosis and into the intrahepatic radicales of the portal vein is illustrated.

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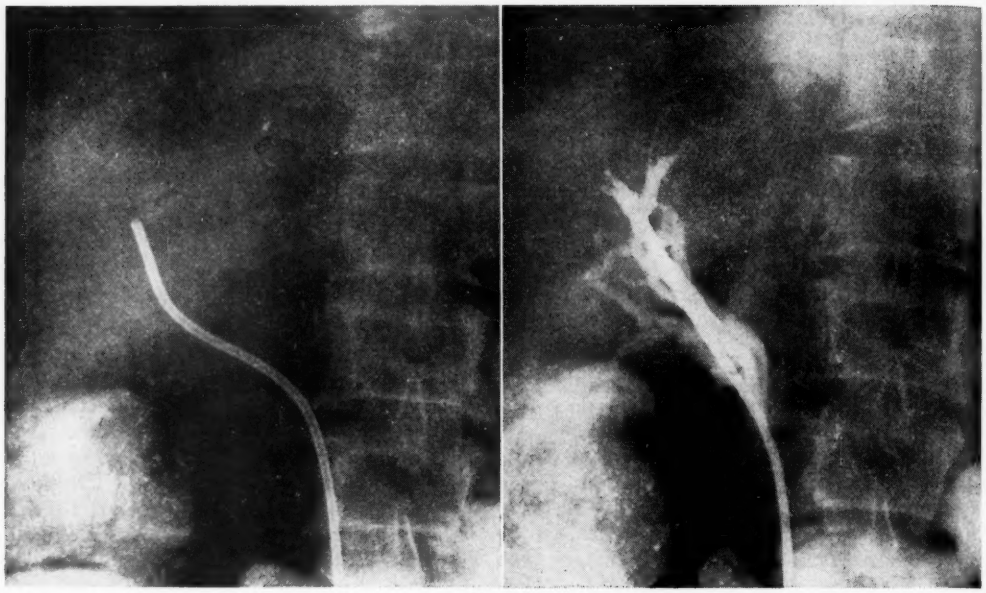
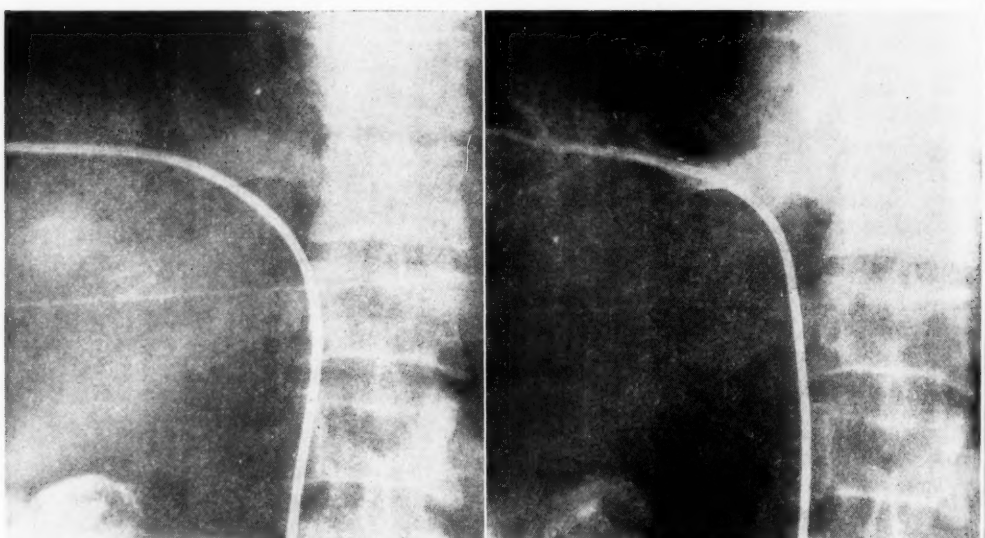


a FIG. 2. b



a FIG. 3. b

FIG. 2. a, Roentgenogram showing typical position of the catheter passing through the portacaval anastomosis and advancing into the wedged portal position. b, With the catheter in the free portal position, radiopaque dye is injected. Note flow of dye away from the liver and into the vena cava.

FIG. 3. a, Cardiac catheter wedged into a small branch of the right hepatic vein. Note position just under diaphragm. b, Right hepatic vein is outlined by radiopaque dye.

principle, to the wedged hepatic venous pressure. After recording the free and wedged pressures, the catheter is adjusted into the free position and blood samples are taken to determine oxygen saturation or other chemical determinations, such as ammonia or bromsulphalein (BSP), as desired. The catheter is then withdrawn into the vena cava and by turning the loop to the right, the right hepatic vein may be entered without difficulty in most instances. The procedure of obtaining the free and wedged pressure and blood sampling is repeated, thus obtaining evaluation of these factors on either side of the hepatic sinusoidal bed.

If the position of the catheter is in doubt in any instance, radiopaque dye may be injected to demonstrate the course of the vein in question. Attempts are made to obtain readings in more than one place on either side of the hepatic parenchyma as variations may occur from one position to another, although usually the difference is not great.

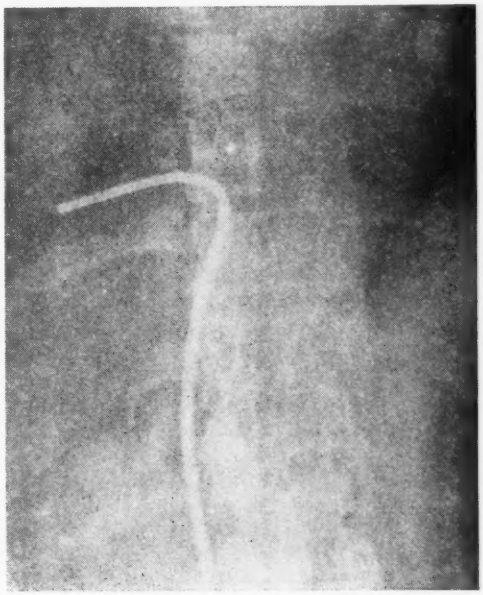


FIG. 4. Roentgenogram showing position of catheter in the right renal vein. Note the difference in angle of entry and in the final position of the catheter when compared with the portal vein. This vein may be differentiated from the right hepatic vein by its more inferior position.

DISCUSSION

The saphenocaval approach is used in the catheterization studies to facilitate passage of the catheter through a side-to-side anastomosis and up into the portal venules within the liver parenchyma. With this technique, it is possible to determine the patency of the anastomosis, the pressure in the free portal vein, and the intrahepatic pressure as reflected in the wedged portal venous pressure. The similarity of wedged pressures from either side has been demonstrated, thus adding support to the significance of these pressures in relationship to the hepatic sinusoidal pressure. However, in those cases in which a high sinusoidal pressure has been maintained after portacaval anastomosis, the wedged hepatic vein pressure has not reflected free portal vein pressure. This has been pointed out previously in a report by Taylor and Myers.

One advantage of the saphenocaval approach in the catheterization studies has been the avoidance of occasional difficulty in not being able to pass the catheter into the inferior vena cava from the right auricle. In addition, it obviates the possibility of the development of cardiac arrhythmia which, although slight, is inherent in the passage of the catheter through the heart. Somewhat to our surprise, it has not been difficult to catheterize the right hepatic vein from the inferior approach. The chief technical problem has been in the obese patient in whom the catheter may not be visualized clearly and, consequently, is more difficult to position accurately.

With the information obtained from such postoperative evaluation, one can generally predict with some confidence the possibility of future bleeding from esophageal varices. If the portal venous pressure is essentially normal, as it was in 6 cases thus far studied, the chance of significant hemorrhage is slight. It is also hoped that the intrahepatic pressures will provide information with regard to long term prognosis in patients undergoing shunting procedures. Although this technique is designed primarily for side-to-side anastomosis, the end-to-side shunt may also be studied by determining free portal pressure through the portacaval anastomosis and hepatic sinusoidal pressure from the right hepatic vein.

SUMMARY

An effective method for the postoperative evaluation of portacaval shunts is presented.

With this technique, the patency of the portacaval anastomosis, the free portal pressure, and the hepatic sinusoidal pressure may be determined.

The saphenocaval approach is superior to the standard brachial technique because: (1) it is simpler to position the catheter as desired; (2) it avoids the possibility of arrhythmia in passing the catheter through the heart; and (3) it allows study of both hepatic and portal venous systems of the liver in side-to-side shunts.

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UMBILICAL HERNIA REPAIR BY LAYER CLOSURE OF POSTERIOR AND ANTERIOR RECTUS SHEATHS

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OPERATION is not always warranted as the treatment in cases of umbilical hernias because many of them seem to disappear spontaneously in infancy and because some that do occur in later life are small, asymptomatic, and insignificant.

Many umbilical hernias are not suitable for the particular technique which is herein described because they are associated with separation of the recti muscles (Fig. 1a).

When the recti muscles are found to be immediately adjacent to the umbilical hernia ring (Fig. 1b), the operative technique to be described may be appropriate.

TECHNIQUE

The medial edges of both recti muscles are exposed by sharp dissection on either side of the defect, and the linea alba above the umbilicus is split into anterior and posterior rectus sheaths, for a distance of a few centimeters (Fig. 2). The repair is then accomplished by suturing the posterior rectus sheath and the anterior rectus sheath separately, leaving the two muscles in contact with each other in the midline. It is not considered wise to suture these muscles together because they normally function separately. Suturing of the rectus sheath may be longitudinal, oblique, or irregular, depending upon the size and the shape of the defect as well as the aponeurotic structures available for closure, using overlapping only when there is a redundancy of tissue.

The transverse skin incision is preferred for cosmetic reasons, either above or below the umbilicus, wherever the normal skin crease lies. The depths of the infolded skin navel are usually excised, leaving an open umbilical dimple which serves as a vent for serosanguinous fluid which might otherwise interfere with healing.

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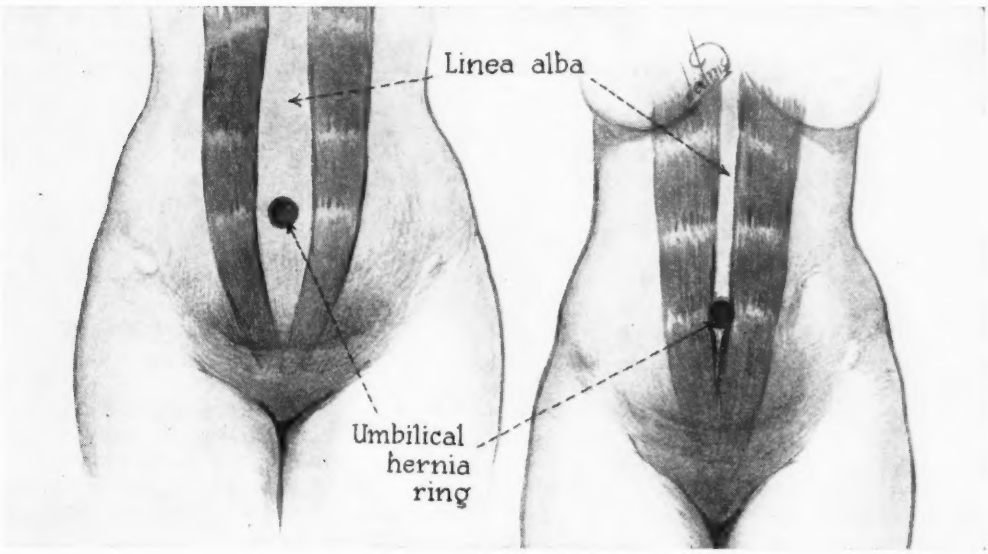

a FIG. 1. b

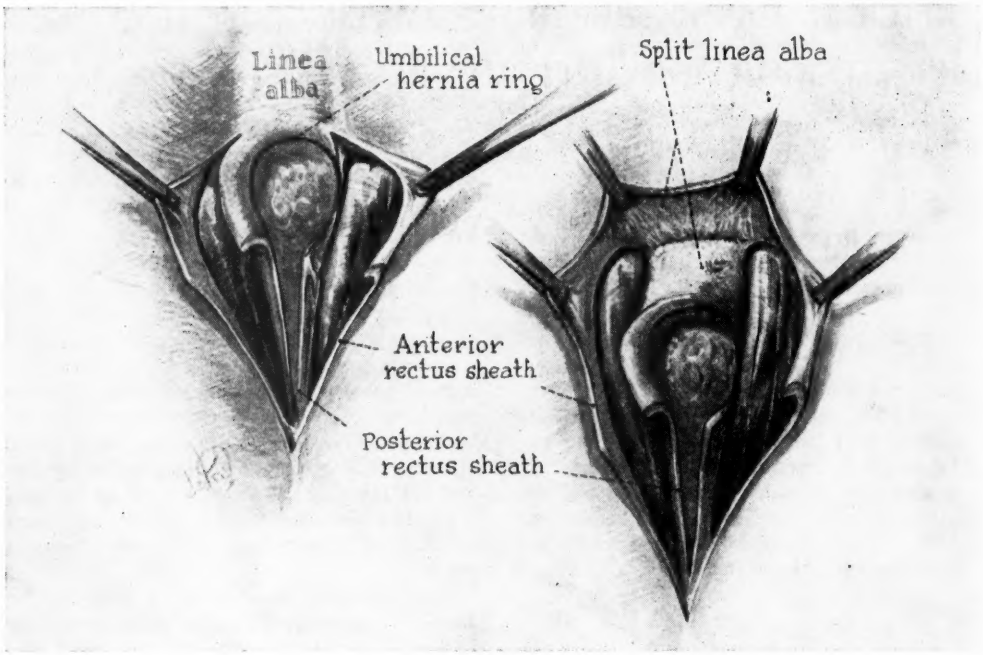

FIG. 2.

The records of 7 recent personal cases are available. In 2 of these instances, the treatment consisted only of purse-string or puckering closure of the umbilical defect. In 2 other cases conventional overlap operations were performed, "vest over pants" and "double breasted coat." In 3 others, the treatment consisted of the technique which is herein described, that is, two-layer closure of the posterior and anterior rectus sheaths.

SUMMARY

A layer closure of posterior and anterior rectus sheaths may be a useful procedure in those cases of umbilical hernia in which the recti muscles are immediately adjacent to the hernia ring.

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LUDWIG G. COURVOISIER AND COURVOISIER'S LAW

LEON MORGENSTERN, M.D., F.A.C.S., New York, New York

ALTHOUGH EVERY MEDICAL STUDENT early becomes aware of Courvoisier's law and every physician sooner or later quotes it as a simple truism, little is known of the "law's" originator. A recent textbook of surgery makes him the national of a country—France—which he not only scarcely visited but even fought against. He receives no attention in any of the standard histories of medicine, nor have any of his works been translated from the original German into English. His law, sign, or phenomenon, often simply stated between quotation marks, is rarely given as he wrote it.

Ludwig G. Courvoisier was born in Basel, Switzerland, in the year 1843. As a boy he apparently was a serious, diligent pupil who early manifested an interest in science, particularly botany. His study of medicine at the University of Basel was almost prematurely terminated by a severe and nearly fatal bout with typhoid. As a medical student he won a prize in a students' competition with a study on "The Histology of the Sympathetic Nervous System." A sojourn in Göttingen for further study was cut short by the Austro-Prussian War.

Upon his return to Basel in 1866, he became assistant to Professor August Socin at the Surgical Clinic of the University. In 1868, he passed his state board and doctoral examination *summa cum laude* with a dissertation on the microscopic structure of the spinal ganglia. He then spent some time traveling, first to London and later to Vienna where he remained for a while with Socin's friend, Billroth, and made friends with Czerny.

From the Department of Surgery, Cedars of Lebanon Hospital, Los Angeles.

The Franco-Prussian War in 1870 again brought the young Courvoisier to the side of Socin, this time as the latter's assistant in the Army Hospital at Karlsruhe. As a reward for his efforts there he received an unexpected appointment as house physician in a newly built hospital in Riehen, just outside Basel. At that time, he was 28 and newly married. While in Riehen, he spent 12 years building a private practice of his own, in addition to his hospital duties. He also found time for a number of community activities and at one point, while convalescing from a severe infection, wrote a book entitled *Nursing of Patients at Home* which was so popular that it went through four reprintings.

In 1883, Courvoisier moved back to Basel where the founding of a private clinic enabled him to practice surgery, as well as carry out his clinical research. His reputation as a surgeon grew rapidly. Aside from his professional duties, he later functioned as President of the Swiss Medical Board and President of the Board of Medical Examiners. He rose in rank at the University Clinic and after Socin's death in 1900, he was offered the directorship, but declined in favor of a younger man.

His most important work was on the surgery of the biliary tract. From his pen flowed a steady stream of publications on diseases of the biliary tract and their surgical management. These writings leave no doubt that he was one of the

pioneers in the definitive treatment of gallbladder disease. He was also among the first to describe choledocholithotomy.

The exposition of the "law" as it is known to us today occurs in a monograph published in 1890, entitled *Pathology and Surgery of the Biliary Tract* (1). In his discussion of common duct obstructions, Courvoisier speaks of the dilatation of the gallbladder and states, ". . . it reacts differently in different types of obstruction. In 109 very well described cases of gallbladder dilatations, only 17 were due to stone obstruction; all the rest being due to occlusions from other causes (10 intrinsic tumors, 8 obliterations, 74 extraluminal compressions). Also, the dilatations caused by stone obstruction were usually only of moderate degree. In only 2 such cases could it be described as markedly dilated. On the contrary, dilatations due to other obstructing causes were quite extensive. . . . Also, diverticuli of the biliary tract as a consequence of bile duct obstruction were never found with calculous obstruction, but only in obstruction due to other causes.

"In contrast to the dilatation of the gallbladder just described, there were 78 cases in which the gallbladder was shrunken, in spite of an obstructed common duct and patent cystic duct. Seventy (90 per cent) of these cases were due to common duct stone, 8 (10 per cent) to other causes of obstruction. Among the latter 8 were 5 in which cholelithiasis was present. . . .

"For this study, I have divided 187 cases into 2 main groups: 87 obstructions due to stone and 100 due to other causes. In those due to stone, 80.4 per cent revealed a shrunken gallbladder and 19.6 per cent revealed a dilated gallbladder. In obstruction due to other causes, the gallbladder is seldom shrunken (8 out of 100 cases), the majority (92 out of 100 cases) being dilated. In other words, *with stone obstruction of the common duct dilatation of the gallbladder is rare. Usually the organ is already shrunken. With obstruction due to other causes, dilatation is most common.* . . .

"Consequently, we have an important diagnostic point in the differential diagnosis of common duct obstruction."

Courvoisier's other medical writings were of little consequence. All were related to clinical observations and statistical case studies. He even wrote a piece on the case of the North American President Garfield. His nonmedical writings reflected his continuing interest in natural history and comprised more than 20 entomologic studies, many colorfully illustrated by himself. In his later years, although his publications diminished in number, he continued the practice of surgery, little affected by the infirmities of age.

On April 8, 1918, at the age of 75, Ludwig G. Courvoisier died in Basel, Switzerland, of pneumonia. His "law" lives on in the strange tenacious immortality of the medical eponym.

REFERENCE

1. Courvoisier, L. G. Kasuistisch-statistische Beiträge zur Pathologie und Chirurgie der Gallenwege. Pp. 57-58. Leipzig: F. C. W. Vogel, 1890.

Reviews of New Books

THE WELL WRITTEN and well illustrated monograph on cancer of the lip[1] reports 907 cases from the National Cancer Institute in Milan covering the period from 1929 to 1956.

This study is a thorough and well organized review of this common malignant disease of the oral cavity. It is divided into 9 major sections. More general aspects, such as location, age, sex, race, predisposing factors, as well as clinical and histopathologic characteristics together with anatomic considerations and lymphatic drainage are discussed before the problem of treatment is considered.

Statistical studies show a 19.7 per cent incidence for regional lymph node metastases. This percentage corresponds with the results in other large series of recent date. The reported figures were not broken down to indicate how many were present upon admission and how many developed subsequently.

Of the 907 patients, 873 received treatment. In 62 per cent, the primary lip lesion was treated by radiation, in 32 per cent by surgery, and in 6 per cent by combined radiosurgical treatment. The results were found to be almost identical for the two principal forms of treatment when carried out adequately; i.e., 62.9 per cent 5 year cures for radiation treatment and 67.5 per cent for surgery. Combined radiosurgical therapy resulted in 54 per cent of 5 year cures.

The section on surgical treatment to which this study is mainly devoted is very adequate. Most of the procedures are illustrated with excellent two-color reproductions showing the progressive sequence in adequate detail. The preoperative and postoperative results are documented with photographs.

The authors dislike the commonly used term "prophylactic" neck dissection and prefer the term "precautionary" instead. They believe that precautionary neck dissections are justified because of the inaccuracy of clinical evaluation as to whether lymph nodes are metastatically involved and because of higher final survival figures. The last point is open to controversy. There does not appear to be any valid or proved evidence that prophylactic neck dissections increase the 5 year survival rate.

As to the indications for the type of neck dissection, the various criteria are outlined. No strict indications for the choice of treatment of the primary lesion are given. The authors emphasize that each case has to be considered individually and a new decision made as to whether surgery or radiation should be employed.

To those interested in plastic surgery and surgery of the head and neck, this should be a valuable book and certainly worth reading. The bibliography is up to date and comprehensive but, unfortunately, not always correct in its data. —*Karl J. Bollinger.*

[1] I TUMORI DEL LABBRO E LA LORO TERAPIA; STUDIO CLINICO E STATISTICO SU 907 CASI DI CARCINOMA LABIALE. By P. Bucalossi, S. Di Pietro, G. F. Lovo, and C. Longa. 104 pages, illustrated. Milan: Casa Editrice Ambrosiana, 1959.

FOR SEVERAL YEARS *Clinical Orthopaedics*[2] has been published to provide original monographs of outstanding interest, and each issue is advertised to contain the complete treatment of a specific subject. This volume consists of Part I of The Hand. It is well bound, excellently printed, and contains splendid reproductions.

The first article is a biography of Sterling Bunnell whose work is so well known in the field of surgery of the hand. The date of his death is incorrect, but otherwise it gives a good account of his life and work. Goff has a delightful article on comparative anthropology of the hand, and Kaplan writes on the anatomy, injuries, and treatment of the extensor apparatus of the fingers. He describes his observations of the normal anatomy as seen on surgical exposure and in the cadaver. Transposing these ideas to the clinical entity of mallet finger, he proposes a method of treatment which is rather different. He immobilizes the finger with the proximal interphalangeal joint in full extension and the distal joint in hyperextension for a period of 5 or 6 weeks. The report does not record the number of patients treated, the results obtained, or the time it took the middle joint of the finger to again become flexible. "Buttonhole" or middle slip ruptures are similarly discussed. His reasoning is hard to follow, and the treatment he recommends is certainly fraught with danger.

There are two nonclinical articles on bones and joints. In one is the statement, "Inspection of a proximal interphalangeal joint after removal of the capsule reveals the cartilage covered distal end of the proximal phalanx and the proximal end of the middle phalanx." One wonders what was expected! Perhaps the footnote "supported in part by Research Grant . . . Public Health Service" explains it.

Hardy reviews adequately the problems involved in covering surface defects of the hand, and there is a plea by McCormack for better training in reconstructive surgery of those dealing with hand injuries.

The article by Mason and Bell on crushing injuries is excellent. In their usual good style and forthright way, they present the problem, outline the basic principles, and show examples of what they mean.

Reconstruction after burns, salvaging the damaged fingertip, and the principles of treating acute trauma are well covered in articles by Goldner, Metcalf, and Flynn, respectively. The latter has changed his ideas in regard to the prophylactic use of antibiotics. Other articles in the issue add little to the standard textbook knowledge of the topics covered by hand surgery.

The report of Miller on "Acute Open Flexor Tendon Injuries" reviews 125 patients treated ac-

[2] CLINICAL ORTHOPAEDICS. Edited by Anthony F. DePalma, the Associate Editors, Board of Advisory Editors, and Board of Corresponding Editors. No. 13, Spring, 1959. 393 pages, illustrated. $7.50. Philadelphia and Montreal: J. B. Lippincott Co., 1959.

cording to the teachings of Koch, Mason, and Allen. The article loses much of its value by conflicting statements and inexcusable errors in reporting the work of others. The results shown are graded as "good" and "poor" and are not accurate enough to justify conclusions as to a better method of treatment.

There is also a short section on general orthopedics and another section containing principally case reports.

Part II of The Hand was scheduled for publication in the fall of 1959. Perhaps a better selection of articles will then justify the claim of a complete treatment of a specific title subject. —*Joseph H. Boyes.*

THE BOOK entitled *The Essentials of Roentgen Interpretation*[3] was designed to bridge the gap between the elementary text and the multiple volume reference work in diagnostic radiology. Roentgenography of the various divisions of the anatomy is discussed briefly. Descriptions of disease processes are concise with clinical and pathologic features limited to the information necessary to clarify the roentgen observations. Positive roentgenologic findings of all the common, and most of the unusual, conditions and diseases are included. Roentgenologic differential diagnosis has been emphasized in the more common diseases. Methods of roentgen-ray examination are described, particularly those dealing with the more complicated procedures such as bronchography, myelography, and pneumoencephalography.

The book is adequately illustrated with numerous excellent reproductions of roentgenograms chosen specifically to illustrate the basic pathologic process. A short, but well selected, up to date bibliography appears at the end of each chapter. This book apparently will fulfill not only the purposes for which it was intended, but it should also serve as a reference source for the practicing physician or surgeon and as a textbook for the undergraduate medical student. Obviously, there are deficiencies which are necessarily inherent in a book presenting a survey of the entire field of diagnostic radiology in a single volume. The discussions are necessarily dogmatic, and many controversial matters have been avoided. Only the more common manifestations of disease have been described.

—*H. L. Steinbach.*

THE SECOND VOLUME of *Progress in Hematology*[4] is designed to bring to the reader a compilation of the more important aspects of advances in hematology. Appearing, as it does, so soon after the publication of the first volume emphasizes the rapid progress which is being made in the many subjects in hematology.

Thirteen topics are reviewed by 20 authors who, in the main, are widely known in the fields which they have reviewed, and the quality of the material presented is generally good. Of especial excellence is the résumé by J. W. Harris of the physical and chemical factors involved in the sickling process. The subjects of kernicterus and hemolytic disease secondary to A-B-O incompatibility are well covered. The use of bone marrow transplants in the experimental animal, discussed by Congdon, points up problems associated with possible human use. A timely review of the humoral factors in erythropoiesis is fairly well summarized by G. Brecher and F. Stohlman, Jr. Bessis has contributed a chapter on hematologic cytology, Finch presents a theoretic consideration of leukemia transmission, and Strumia reviews the practical aspects of blood preservation. Myleran therapy for chronic granulocytic leukemia is discussed by the English authors, Wilkinson and Turner. Wilkinson is known for his original work with B-chlorinated alkyl amines and his subsequent investigations of the clinical effectiveness of various types of chemotherapy. The material on the possible significance of lipid anticoagulants is reported upon by the editor of this volume and his co-workers. The hematologic aspects of serotonin, platelet transfusions in hemorrhagic states, and the surgical approach to esophageal varices are discussed respectively by M. B. Zucker, Cronkite and Jackson, and Ripstein.

This book thus contains something of interest to several disciplines. However, its chief purpose best subserves the internist and hematologist, and as such is recommended to those with these interests.

—*Walter A. Rambach.*

REPORTED IN THE VOLUME entitled *Low Intensity Radium Therapy*[5] are the personal experiences of the authors' development of the interstitial use of radium needles in the treatment of accessible cancers, and their success with this method. There have been many excellent results, and the work is documented by 114 case reports.

The needles used contain from .6 to 3 milligrams of radium and vary in length from 11 to 60 millimeters. "As a rule, the needles are placed parallel to one another about 1 cm. apart in rows designed to deliver a cancerocidal dose into and well outside the palpable tumor." The needles are usually left in place for 7 days and nights.

The authors believe that better results are obtained from the use of low strength needles for a longer period, than from higher strength needles for a shorter period. They also believe that results following interstitial radiation therapy of accessible cancer are more favorable, with less damage to uninvolved structures, than they are following external x-ray or supervoltage therapy. There is little doubt that few therapists administering x-ray or supervoltage therapy can obtain as many dramatic results from treatment of local cancers about the face and mouth.

Those surgeons who are familiar only with the results of surgical resection, or external radiation, of these primary lesions should take this opportunity to see and to study the good results which can be obtained often by the skillful use of interstitial radiation.

It might be recommended, parenthetically, that every radiotherapist treating such cancers should be

[3]THE ESSENTIALS OF ROENTGEN INTERPRETATION. By Lester W. Paul, M.D., and John H. Juhl, M.D. 839 pages, 1203 illustrations. $25.00. New York: Paul B. Hoeber, Inc., Med. Book Dept. of Harper & Bros., 1959.

[4]PROGRESS IN HEMATOLOGY. Edited by Leandro M. Tocantins, M.D. With 19 contributors. Vol. II. 290 pages, illustrated. $9.75. New York and London: Grune & Stratton, Inc., 1959.

[5]LOW INTENSITY RADIUM THERAPY. By Charles L. Martin, E. E., M.D., F.A.C.R., and James A. Martin, M.D., F.A.C.R. 256 pages, 118 black and white illustrations and 20 color plates. $12.50. Boston and Toronto: Little, Brown & Co., 1959.

familiar with the excellent results often obtained now by modern surgery, and especially of the extreme difficulties encountered in attempts to follow radiation by surgery—either for repair or cure. The authors state with regard to the surgeon: "We prefer to enlist his services only where irradiation fails to control those carcinomas for which it offers a chance of cure."

Possibly, the most controversial section of the book is that in which radiation therapy is recommended for metastatic carcinoma in the lymph nodes of the neck. Probably few physicians, radiologists, or surgeons will agree with this recommendation.

Interstitial radiation is a most useful method in the treatment of many primary cancers of the mouth, face, skin, and other areas. The authors have been pioneers in developing this tool and in bringing about such a high degree of effectiveness with its use. This book will be both valuable and interesting to all who undertake the treatment of these lesions.

—*Frank McDowell.*

THE EDITOR and the contributing authors of the new edition of *Cole & Elman's Textbook of Surgery*[6] have done an excellent job in bringing its contents up to date without expanding it beyond its primary purpose, a textbook for students. The many important contributions to the knowledge of surgery since publication of the last edition in 1952 necessitated not only extensive revision of the text but, also, the addition of two essentially new chapters devoted to the recently developed field of cardiovascular surgery. This subject is unusually well presented as are others, notably: laboratory aids, cancer, and fluid electrolyte and caloric balance.

The current edition also contains two entirely new and interesting chapters. One, entitled, "A Brief Background of Surgery," is well composed and gives an historical discussion which appropriately introduces the text. The other chapter deals with medical ethics and conduct, an often neglected part of the medical student's education. —*J. Dewey Bisgard.*

IT IS INDEED A PLEASURE to note the appearance of the third edition of Clement Smith's book *The Physiology of the Newborn Infant.*[7] This new volume has been greatly expanded. The bibliographies at the end of each of the individual chapters have been combined and placed at the end of the book.

As in previous editions, Smith has drawn heavily upon the data accumulated by his own research group at the Boston Lying-In Hospital. Much new material collected since 1951 has been added. He has also placed great emphasis upon the work done by Geoffrey Dawes at Oxford and by Professor McCance at Cambridge. In fact, his comprehensive review of the articles on the newborn published by authors from Western Europe constitutes one of the most useful and attractive features of this new edition.

Smith is at his best in the chapters on respiration since much of the work had been done in his own laboratory. Much information has been included about the new thinking which has developed regarding the adjustments of the circulatory system after birth. The sections on the physiology of the digestive tract and regulation of water and electrolytes are most helpful.

There could have been more material included in the discussion upon the physiologic changes of the central nervous system during the newborn period. In particular, some of the available data on the blood-brain barrier should have been reviewed. One also would liked to have found a more comprehensive report upon the development of cellular metabolism in the fetus and newborn. The newer developments in the glucuronyl transferase and phenylalanine-tyrosine enzyme systems are touched upon only briefly. The problem of transport across membranes also could have been given in more detail.

The author has again succeeded in confining the monograph to purely physiologic observations and has wisely avoided discussion about the effects of therapy upon these changes which has often been cause for confusion in the literature. The contents of this volume should be of fundamental importance to all pediatricians and obstetricians.

—*David Yi-Yung Hsia.*

IN RECENT YEARS there has been an ever increasing use of foreign materials for the repair and replacement of defective parts of the human body. Substitutes for heart valves, arteries, and hip joints have been designed, fabricated, and inserted with early results which were dramatically successful. Failure may have been due to poor choice of materials, to poor design, or to poor surgical technique. Now, we have for the first time a reference work upon the use of metals in bone and joint surgery. This book, *Metals and Engineering in Bone and Joint Surgery,*[8] brings to the surgeon information regarding metallurgy including metal behavior—the corrosion process—available metals, metallic transfer, and the use and care of metals destined to be buried in the human body. The second part of the book is devoted to an explanation of some biomechanical principles which are important in the field of bone and joint repair.

A remarkable amount of helpful information is packed into the pages of this book, and much useless material has been omitted. There are some minor errors which do not detract from the great value of this pioneering effort. It should be required reading for every surgeon who introduces bone plates and screws and for every manufacturer of metallic surgical materials. —*Joseph S. Barr.*

A MORE EXTENSIVE TREATISE on pediatric anesthesia than has previously been available is presented in the volume *Anesthesia for Infants and Children.*[9] Basic anes-

[6] COLE & ELMAN'S TEXTBOOK OF SURGERY. By Warren H. Cole, M.D. With 49 contributing authors and consultants. Foreword by Evarts A. Graham. 7th ed. 1224 pages, illustrated. $17.00. New York: Appleton-Century-Crofts, Inc., 1959.

[7] THE PHYSIOLOGY OF THE NEWBORN INFANT. By Clement A. Smith, M.D. 3rd ed. 497 pages, illustrated. $12.50. Springfield, Ill.: Charles C Thomas, 1959.

[8] METALS AND ENGINEERING IN BONE AND JOINT SURGERY. By Charles Orville Bechtol, M.D., Albert Barnett Ferguson, Jr., M.D., and Patrick Gowans Laing, M.B., B.S., F.R.C.S. 186 pages, 119 illustrations. $8.00. Baltimore: The Williams & Wilkins Co., 1959.

[9] ANESTHESIA FOR INFANTS AND CHILDREN. By Robert M. Smith, M.D. Foreword by Robert E. Gross, M.D. 418 pages, 182 illustrations. $12.00. St. Louis: The C. V. Mosby Co., 1959.

thetic management of pediatric patients is extensively covered. In addition, the problems of surgery, the surgical disease, and incidental complicating diseases are related to the preoperative, operative, and postoperative anesthetic management. This is a refreshing approach from the usual trite discussions of anesthesia for this and that disease. Discussions of oxygen therapy, resuscitation, and fluid therapy complete the concept of total patient care. On the basis of these very able presentations, this book, no doubt, will be a valuable reference work for the practicing anesthesiologist. For the student of anesthesiology, the chapters on "Biology and Behavior, or Factors Determining the Child's Response to Anesthesia," "Respiratory Physiology in Infants and Children," and "Fluid Therapy and Blood Replacement" should prove particularly valuable for background study.

The author refers liberally to his own broad experience at the Children's Medical Center in Boston. Rather than being redundant or burdensome, this personal touch lends substance to his conclusions. The author's personal preference is given for agent and technique in particular situations and should be a useful guide in selected cases. The reader must understand that all anesthesiologists may not necessarily subscribe to the author's choices, and that there may be many other equally good ways of accomplishing the same objective.

The print is easy to read, and the illustrations and tables are appropriate, effectively arranged, and easily followed. Few typographic errors are apparent. The index is not extensive, but adequate for most purposes. Bibliographic references are given to major original sources and should provide a starting point for one interested in a more thorough review of the literature.

In summary, this work should be an excellent text for the student beginning pediatric anesthesia and an equally excellent source of reference for the practitioner confronted with an unusual problem or complication in the pediatric patient.

—*W. Curtis Pearcy.*

SELDOM DOES one complete the review of a book with the feeling of wholehearted endorsement as is occasioned in the instance of *The Care of Minor Hand Injuries*.[10]

The author has most successfully answered the usual questions raised by the average surgeon engaged in the repair of "run of the mill" hand injuries which can be taken care of on an outpatient basis. While maintaining emphasis on general principles, the book also includes important step-by-step details so necessary for the successful completion of any given technique. Of particular value is the material given in the section on Principles of Care, and if the reader keeps this information well in mind the understanding of the treatment of specific injuries will be materially enhanced. The text is well arranged for ready reference, written in a pleasing style, and sufficiently comprehensive in scope as to be of value to all surgeons participating in, or entering, this field of reconstructive repair.

If the author feels subject to "jennerian criticism" for writing this book, as he suggests in the preface, he may rest assured that he is not forcing this information on the profession but, rather, supplying them with the information which they have long been asking for.

—*L. D. Howard, Jr.*

COMPLETE ABSTRACTS of the significant articles on cancer which appeared in the literature during the preceding year are presented in *The Year Book of Cancer*.[11] The 128 members of the editorial board are divided into 24 groups, each relating to some field in oncology. Each group contains physicians or other medical specialists of various disciplines. The author of an article selected for inclusion was asked to prepare an abstract for *The Year Book* and, in most cases, the author complied. In this manner, the members of the editorial board selected 298 articles from approximately 4,000 published during the preceding year. Two-thirds of the abstracts are of articles which appeared in American journals, the remaining one-third are from foreign journals. This third volume has been achieved by the concerted efforts of 419 persons and represents the work published in 160 journals.

The contents are arranged according to organ systems such as head and neck, skin and breast, but what is perhaps of special interest are the chapters on "Chemotherapy and Hormone Therapy," "Biochemistry, Physics, and Radiobiology," "Bacteriology, Immunology, and Virology" as well as a chapter on "General Animal Tumors."

No attempt will be made to abstract the abstracts; however, in the chapter on "Chemotherapy and Hormone Therapy" an interesting article by Kennedy on the present status of hormone therapy in advanced breast cancer will be of interest to many. Included in the comments by Moore and Kondo on the National Clinical Adjuvant Chemotherapy Program are short paragraphs on the following topics: therapy of unestablished tumor cells; effect of delay in giving chemotherapy; importance of routes of drug administration; adverse effects of chemotherapeutic agents; and chemotherapy as a surgical adjuvant. There is also an abstract of an article by Shimkin and Moore on the Adjuvant Use of Chemotherapy in Surgical Treatment of Cancer.

In the chapter on "Reconstruction and Rehabilitation" is an abstract on Host-Tumor Antagonism by Pelner. The problem of production of antibodies to cancer is discussed with the endocrinologic aspects of cancer. In the section on "Advanced Tumors and Terminal Care," is an abstract of an article on Dissemination of Cancer Cells by Cole and his associates.

The book consists of 570 pages, printed on excellent paper, and it contains an adequate number of illustrations. It represents a splendid effort to gather current developments in a vast field into one handy volume.

—*John Schneewind.*

[10] THE CARE OF MINOR HAND INJURIES. By Adrian E. Flatt, M.A., M.D., F.R.C.S. Foreword by Carroll B. Larson, M.D. 266 pages, illustrated. $9.50. St. Louis: The C. V. Mosby Co., 1959.

[11] THE YEAR BOOK OF CANCER (1958–1959 YEAR BOOK SERIES). Compiled and edited by Randolph Lee Clark, Jr., B.S., M.D., M.Sc. (Surgery), D.Sc. (Hon.), and Russel W. Cumley, B.A., M.A., Ph.D. 570 pages, 202 illustrations. $8.00. Chicago: The Year Book Publishers, Inc., 1959.

THE EDITED PROCEEDINGS of a three day conference held at the College of Medicine of the University of Utah in January 1959, under the sponsorship of The Hematology Study Section, Division of Research Grants, National Institutes of Health, are given in the volume entitled *The Kinetics of Cellular Proliferation.*[12] The scope of the conference was unusually broad covering a wide range of topics of varying degrees of complexity. The present volume seems to have skillfully reproduced the flavor of the meeting by adherence in print to the actual format of the conference. Thus, 40 separate articles dealing with problems and techniques related to an understanding of the kinetics of cellular proliferation, together with their attendant and respective discussions, are divided and presented under six section headings: I. The Use of Classic Morphologic Techniques; II. Deoxyribonucleic Acid Synthesis Stability and Degradation; III. Studies with DNA Labels; IV. Studies on Leucocyte and Platelet Production; V. Kinetics of the Regulation of Red Cell Production; and VI. Mathematical Considerations.

Many of the authors, conference participants, are nationally or internationally known for their work in the kinetics of cell proliferation. Their reputations are reflected in the high quality of the material and the animated and informative discussions.

By virtue of its ease of access and manipulation, but certainly not by virtue of its simplicity, the hematologic system is primarily concerned in these studies. This does not circumscribe the value of the work; for the implications and applications of some of the techniques utilized and results obtained are manifold in their relation to other tissues. For instance, the discussions relevant to thymidine and thymidylic acid synthesis and their relation to desoxyribose nucleic acid reutilization and tritium labeling are pertinent to the study of any system of cellular proliferation.

This is a book of some basic importance. It represents the most complete and up to date compilation of material and thought relevant to methods for the study of cell division and maturation and, brings under one heading, the leading concepts that have developed from the use of these techniques. Some of the methods of study involving mathematic models, biostatistics, and analogic computers border on the esoteric. But so long as man is still required to program a computer we may be assured that the data are not absolute and that human fallibility remains with us in research.

There are no significant typographic errors in the book. The references are abundant. Charts, graphs, and photomicrographs are reproduced excellently. This volume is wholeheartedly recommended to those who would understand cell formation and cell disorders. It should be of immediate usefulness to the hematologist and oncologist. —*Walter A. Rambach.*

A RATHER COMPLETE ATLAS, *Roentgen Diagnosis in the Newborn and Infants*[13] covers all of the systems but is confined to this early age period. The material ranges from the normal and its variations to most of the known pathologic conditions.

The roentgenograms are printed in the positive. This is at first slightly disturbing, but the superb reproductions make up for this minor inconvenience. Even with a minimum facility in the German language, the reader can gain considerable knowledge about normal and pathologic conditions during this period of life. Certainly, for those having little contact with infants it is a fine reference book.

A thorough knowledge of German makes this book an invaluable asset in pediatric radiology but even a passing knowledge of the language makes thumbing through it worth while. —*Harvey White.*

THE MONOGRAPH entitled *Mitral Valvulotomy*[14] reports experience only with patients undergoing this operation at the Cornell Medical Center from 1951 to 1956. It is not a comprehensive study of the subject, but rather a clinical report which is similar, but longer, and usually in greater detail than reports found in medical journals concerning the experience of other clinics with this operation.

The book is divided into three parts. The first part describes the first 100 patients, the second part describes the second and third 100 patients, and the third part returns again to the first 100 patients and describes their long term follow-up period. This organization—justification for which is not clear in the reviewer's mind—makes the presentation unduly long through repetition in each of the three sections.

There is no comparison of the results described here with those reported from other clinics, and a list of references on the subject is far from complete. Evaluation of the patient is on clinical grounds with no physiologic studies. Matters of great current interest such as combined operations on more than one valve, open surgery, surgery for insufficiency, and valve replacement are ignored or merely mentioned.

—*F. John Lewis.*

THE PRIMARY AIM of the attractive monograph, *Principles and Practice of Obstetric Anesthesia,*[15] is to present an evaluation of the range of methods of obstetric anesthesia and analgesia with reference to the physiologic and pharmacologic processes involved. Well written, in a scholarly manner, it fulfills the author's purpose.

Although the presentation is from the British viewpoint, differences in North American practice are indicated, and there is much helpful information which should be of value to practitioners on both sides of the Atlantic. The material is organized under headings of mother, placenta, analgesia, indications for anesthesia, the newborn, and equipment and procedures. Chapters of particular interest are those dealing with the important anatomic and physiologic considerations of pregnancy and labor relative to the practice of anesthesia; placental function, the crux of most problems

[12]THE KINETICS OF CELLULAR PROLIFERATION. Edited by Frederick Stohlman, Jr., M.D. 456 pages, illustrated. $5.75. New York and London: Grune & Stratton, 1959.

[13]ROENTGENDIAGNOSTIK BEIM NEUGEBORENEN UND SAEUGLING. By Hermann G. Wolf. Foreword by Prof. Dr. K. Kundratitz. 317 pages, 370 illustrations. $23.60. Wien: Verlag Wilheim Maudrich, 1959.

[14]MITRAL VALVULOTOMY. By Harold J. Stewart, M.D., and Frank Glenn, M.D. 244 pages, 25 illustrations. $10.50. Springfield, Ill.: Charles C Thomas, 1959.

[15]PRINCIPLES AND PRACTICE OF OBSTETRIC ANAESTHESIA. By J. Selwyn Crawford, M.B., Ch.B., D.A. (Eng.), F.F.A.R.C.S. 128 pages, illustrated. $4.00. Springfield, Ill.: Charles C Thomas, 1959.

in obstetric anesthesia; and important physiologic aspects of neonatal respiration and circulation. A rather extensive list of references is included at the end of each chapter. In both the introduction and the epilogue, the current deficiencies in anesthesia service not only in hospitals but also in domiciliary obstetrics are deprecated and suggestions are made for improvement.

Paper and printing are of good quality and all who are interested in obstetric anesthesia from the physiologic and pharmacologic standpoint will find this a valuable text. —*Mary Frances Poe.*

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgement must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

PRAKTISCHE SPERMATIOLOGIE EIN LEITFADEN FUER AERZTE. By Priv. Doz. Dr. Med. H. W. Vasterling. 224 pages, 86 illustrations. $6.40. Stuttgart: Georg Thieme, 1960.

THE PLACENTA AND FETAL MEMBRANES. Edited by Claude A. Villee. 404 pages, illustrated. $10.00. Baltimore: The Williams & Wilkins Co., 1960.

PROSTHETIC PRINCIPLES—ABOVE KNEE AMPUTATIONS. By Miles H. Anderson, Ed.D., John J. Bray, C.P., C.O., Charles A. Hennessy, C.P., C.O. Edited by Raymond E. Sollars, 331 pages, illustrated. $10.00. Springfield, Ill.: Charles C Thomas, 1959.

CINEFLUOROGRAPHY. Proceedings of the First Annual Symposium on Cinefluorography, Sponsored by the Department of Radiology, University of Rochester, School of Medicine and Dentistry, Rochester, New York, Friday and Saturday, November 14 and 15, 1959. Edited by George H. S. Ramsey, M.D., Theodore A. Tristan, M.D., James S. Watson, Jr., M.D., Sydney Weinberg, and William S. Cornwell, M.A. 266 pages, illustrated. Springfield, Ill.: Charles C Thomas, 1959.

AN INTRODUCTION TO GYNECOLOGICAL EXFOLIATIVE CYTOLOGY; A MANUAL FOR CYTOTECHNICIANS. By Winifred Liu, M.Sc., M.D. 127 pages, 44 illustrations. $6.00. Springfield, Ill.: Charles C Thomas, 1959.

CLINICAL ORTHOPAEDICS. Edited by Anthony F. DePalma. No. 15, Winter, 1959. 217 pages, illustrated. $7.50. Philadelphia and Montreal: J. B. Lippincott Co., 1959.

MEDIEVAL AND RENAISSANCE MEDICINE. By Benjamin Lee Gordon, M.D. 843 pages, illustrated. $10.00. New York: Philosophical Library, Inc., 1959.

THE TREATMENT OF BRONCHIAL NEOPLASMS. By Robert R. Shaw, M.D., and Donald L. Paulson, M.D. 135 pages, illustrated. $8.00. Springfield, Ill.: Charles C Thomas, 1959.

SURGICAL TREATMENT OF BONE AND JOINT TUBERCULOSIS. By Robert Roaf, M.Ch.(Orth.), F.R.C.S.(Ed.), F.R.C.S.(Eng.), W. H. Kirkaldy-Willis, M.D.,B. Chir., F.R.C.S.(Ed.), and A. J. M. Cathro, M.B., Ch.B. 137 pages, 90 illustrations. $7.00. Edinburgh and London: E. & S. Livingstone Ltd., 1959. Baltimore: The Williams & Wilkins Co., exclusive U. S. agents.

TREATMENT OF CANCER IN CLINICAL PRACTICE. Edited by Peter B. Kunkler, M.D.(Cantab.), M.R.C.P., F.F.R., and Anthony J. H. Rains, M.S.(Lond.), F.R.C.S. 821 pages, illustrated. $19.00. Edinburgh and London: E. & S. Livingstone Ltd., 1959. Baltimore: The Williams & Wilkins Co., exclusive U. S. agents.

SURGERY AS A HUMAN EXPERIENCE; THE PSYCHODYNAMICS OF SURGICAL PRACTICE. By James L. Titchener, M.D., and Maurice Levine, M.D. 285 pages. $6.00. New York: Oxford University Press, 1960.

STRAHLENBIOLOGIE, STRAHLENTHERAPIE, NUKLEARMEDIZIN UND KREBSFORSCHUNG; ERGEBNISSE 1952–1958. Compiled by G. Barth, J. Becker, U. Cocchi, U. Feine, H. Fritz-Niggli, F. Gauweky, W. Harm, W. Hellriegel, W. Horst, O. Hug, R. W. Kaplan, K. H. Kärcher, R. Koch, H. Langendorff, H. Nachtsheim, W. Pohlit, K. Sommermeyer, G. Weitzel, and R. Wideröe. 998 pages, illustrated. $65.50. Stuttgart: Georg Thieme, 1959.

LEHRBUCH DER GYNAEKOLOGIE FUER STUDIUM UND PRAXIS. By Professor Dr. Med. Robert Schröder. 506 pages, illustrated. Leipzig: Georg Thieme, 1959.

SUI TUMORI PRIVITIVI DEL CERVELLETTO; STUDIO ANATOMO-ISTOPATOLOGICO SU 110 NEOPLASIE CEREBELLARI. By F. Gullotta and G. Spigolon. 72 pages, illustrated. Modena, Italy: Societa Tipografica Editrice Modenese, 1959.

L'OSTRUZIONE INTESTINALE (FISIOPATHOLOGIA E CLINICA). By Prof. Edmondo Malan. 311 pages, 65 illustrations. Roma: Edizioni Mediche e Scientifiche, 1959.

ARCHIVIO "PUTTI" DI CHIRURGIA DEGLI ORGANI DI MOVIMENTO. Bibliographia 1956. Directed by D. Casuccio and O. Scaglietti. Edited by L. Gui. Vol. XI. 447 pages, illustrated. Firenze: Edizioni Scientifiche dell "Istituto Ortopedicao Toscano," 1959.

THE PRESIDENT'S REVIEW INCLUDING A QUARTER CENTURY IN THE NATURAL SCIENCES. By Warren Weaver. From the Rockefeller Foundation Annual Report 1958. 168 pages, illustrated. New York: The Rockefeller Foundation, 1959.

ARTERIOPATIE OBLITERANTI DEGLI ARTI INFERIORI. By G. Marcozzi, S. Messinetti, and G. A. Ricci. 195 pages, illustrated. Roma: Edizioni Mediche e Scientifiche, 1959.

ISTITUTO DE CLINICAL CHIRURGICA GENERALE E TERAPIE CHIRURGICA DELL' UNIVERSITA DE PERUGIA. Direttore: Prof. Giovanni Marcozzi. La flebografia vertebrale transomatica originale metodica d'indagine angiografica dei plessi rachidei e aziogos-cavali. By G. Marcozzi, S. Messinetti, L. Saracca, and M. Colombati. 159 pages, illustrated. Roma: Edizioni Mediche e Scientifiche, 1959.

DER PLATTFUSS KLINIK, PATHOLOGIE KONSERVATIVE UND OPERATIVE BEHANDLUNG. By Kaspar Neiderecker. 368 pages, illustrated. Stuttgart: Ferdinand Enke, 1959.

UNIVERSITÀ DEGLI STUDI DE MILANO. Istituto de Patologia Speciale Chirurgica. Direttore: Prof. Armando Trivellini. I diverticoli dell' esofago. By Giulio R. Bettolo and Guido Franzini. 203 pages, illustrated. Milano: Unione Tipografica, 1959.

ATTI DELLA SOCIETA LOMBARDA DI SCIENZE MEDICO-BIOLOGICHE. Supplemento. Volume XIV, Anno 1959. Simposio sulla tripsina e chimotripsina. 235 pages, illustrated. Milano: Edizioni Minerva Medica, 1959.

DER ENDOGENE JODHAUSHALT DES MENSCHEN UND SEINE STOERUNGEN. By Dozent Dr. Erich Klein. 171 pages, 35 illustrations. $5.70. Stuttgart: Georg Thieme, 1960.

THE STORY OF DISSECTION. By Jack Kevorkian, M.D. 80 pages, illustrated. $3.75. New York: Philosophical Library, Inc., 1959.

MANAGEMENT OF THE AGED SURGICAL PATIENT. By Sidney E. Ziffren, M.D., 219 pages, 30 illustrations. $7.50. Chicago: The Year Book Publishers, Inc., 1960.